Lessons from the ICU
Under the Auspices of the European Society
of Intensive Care Medicine

Maurizio Cecconi, Head Dept Anesthesia and ICU,
Humanitas Research Hospital,
Rozzano, Milano, Italy *Series Editor*

Daniel De Backer, Dept Intensive Care Erasme University,
Université Libre de Bruxelles, Bruxelles,
Brussels Hoofdst.ge., Belgium *Series Editor*

Jean-Charles Preiser
Margaret Herridge
Elie Azoulay
Editors

Post-Intensive Care Syndrome

Springer

Editors
Jean-Charles Preiser
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

Elie Azoulay
Medical Intensive Care Unit
AP-HP Saint-Louis Hospital
Paris, France

Margaret Herridge
Respiratory and CCM
Toronto General Hospital
University of Toronto
Toronto, ON, Canada

ISSN 2522-5928 ISSN 2522-5936 (electronic)
Lessons from the ICU
ISBN 978-3-030-24249-7 ISBN 978-3-030-24250-3 (eBook)
https://doi.org/10.1007/978-3-030-24250-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Until relatively recently, our role as intensivists focused solely on managing patients within the intensive care unit (ICU), with little (if any) thought about the patient's post-ICU discharge course. We were happy if the patient survived their critical illness and reached a stage where they could be discharged! In recent years, however, we have begun to be increasingly aware of the long-term outcomes of ICU patients – the physical, cognitive, and/or psychological problems that are encountered by many patients for months and even years after their ICU discharge. The psychological impact of critical illness on family members is also a concern, with many close relatives suffering symptoms of anxiety, posttraumatic stress, and depression for many years after the discharge of their loved one.

Importantly, many of these post-ICU complaints could be reduced with improved patient management during the ICU admission. Less sedation, more careful use of medications known to impact long-term outcomes such as corticosteroids, earlier mobilization, improved nutritional support, better communication, and involvement of family members are some examples of approaches that can help limit the development and severity of post-ICU complications and improve post-ICU quality of life. As intensivists, we need to think not just about survival per se but also about the quality of that survival to reflect on how our interventions may impact the health and well-being of each patient and their family after discharge.

As the demand for intensive care increases and ICU mortality rates decreases, so the population of ICU survivors is also increasing, carrying with it an urgent need to heighten awareness of post-intensive care syndrome, improve our understanding of the underlying mechanisms and causes, and determine how best to prevent and treat these complications. This book, written by international experts in this field, is therefore an important and timely volume and of value for all intensivists as we strive to maximize long-term, quality-of-life outcomes for our patients and their families.

Jean-Louis Vincent, MD, PhD
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

Contents

III Cognitive/Psychological Impairment

IV Rehabilitation

Contributors

Yasmine Ali Abdelhamid
Intensive Care Unit, Royal Melbourne Hospital
Parkville, VIC, Australia

Melbourne Medical School
University of Melbourne
Parkville, VIC, Australia

Discipline of Acute Care Medicine
University of Adelaide
Adelaide, SA, Australia
yasmine.aliabdelhamid@mh.org.au

Abdulrahman A. Al-Fares
Adult Critical Care Medicine
Fellowship Program, University of Toronto
Toronto, ON, Canada

Al-Amiri Hospital, Ministry of Health
Kuwait City, Kuwait

Interdepartmental Division of Critical Care
Medicine, University of Toronto
Toronto, ON, Canada

Toronto General Hospital
Toronto, ON, Canada
abdulrahman.al.fares@mail.utoronto.ca

Elie Azoulay
Medical Intensive Care Unit
AP-HP Saint-Louis Hospital
Paris, France

Critical Care Department, St-Louis Hospital,
ECSTRA Team, and Clinical Epidemiology, UMR
1153 (Center of Epidemiology and Biostatistics
Sorbonne Paris Cité, CRESS), INSERM, Paris
Diderot Sorbonne University
Paris, France
elie.azoulay@aphp.fr

J. Batt
Department of Medicine and the Keenan
Research Center for Biomedical Science
St. Michael's Hospital
Toronto, ON, Canada

Institute of Medical Science
University of Toronto
Toronto, ON, Canada

Interdepartmental Division of Critical Care
University of Toronto
Toronto, ON, Canada
jane.batt@utoronto.ca

Danielle E. Bear
Departments of Nutrition and
Dietetics and Critical Care
Guy's and St Thomas' NHS Foundation Trust
London, UK
Danielle.Bear@gstt.nhs.uk

Stephen J. Brett
Department of Surgery and Cancer
Imperial College London
London, UK

Imperial College Healthcare NHS Trust
Hammersmith Hospital
London, UK
stephen.brett@imperial.ac.uk

Nathan E. Brummel
The Ohio State University
Wexner Medical Center
Columbus, OH, USA
nathan.brummel@osumc.edu

K. J. Burdick
Neuroscience, Vanderbilt University
Nashville, TN, USA
kendall.burdick@vanderbilt.edu

Lee-anne Chapple
Intensive Care Research
Royal Adelaide Hospital
Adelaide, South Australia
lee-anne.chapple@adelaide.edu.au

B. Clerckx
Faculty of Movement and Rehabilitation Sciences, Department Rehabilitation Sciences, KU Leuven
Leuven, Belgium

Division of Critical Care Medicine
University Hospitals Leuven
Leuven, Belgium
beatrix.clerckx@uzleuven.be

Evelyn J. Corner
Department of Clinical Sciences
Brunel University London
Uxbridge, UK

Therapies Department, The Royal Brompton and Harefield NHS Foundation Trust
London, UK
Evelyn.Corner@brunel.ac.uk

M. C. Courtney
Department of Medicine
Health and Society, Vanderbilt University
Nashville, USA
madison.c.courtney@vanderbilt.edu

B. H. Cuthbertson
Department of Critical Care Medicine
Sunnybrook Health Sciences Centre
Toronto, ON, Canada
brian.cuthbertson@sunnybrook.ca

Adam Deane
Intensive Care Unit, Royal Melbourne Hospital
Parkville, VIC, Australia

Melbourne Medical School,
University of Melbourne
Parkville, VIC, Australia

Discipline of Acute Care Medicine
University of Adelaide
Adelaide, SA, Australia
Adam.Deane@mh.org.au

Audrey de Jong
Anesthesia and Critical Care Department,
CHU Montpellier, Montpellier, France

Department of Anesthesia and Intensive Care unit
Regional University Hospital of Montpellier,
St-Eloi Hospital, PhyMedExp, University of Montpellier, INSERM U1046
Montpellier, France
a-de_jong@chu-montpellier.fr

Ingeborg M. Dekker
Department of Nutrition and Dietetics
Internal Medicine
VU University Medical Center Amsterdam
Amsterdam, The Netherlands
im.dekker@vumc.nl

C. C. dos Santos
Department of Medicine and the Keenan Research Center for Biomedical Science
St. Michael's Hospital
Toronto, ON, Canada

Institute of Medical Science
University of Toronto
Toronto, ON, Canada

Interdepartmental Division of Critical Care
University of Toronto
Toronto, ON, Canada
DosSantosC@smh.ca

Hans Flaatten
University of Bergen
Department of Clinical Medicine
Berge, Norway

General ICU, Haukeland University Hospital
Bergen, Norway
Hans.Flaatten@uib.no

Pamela Flood
Stanford University
San Francisco, CA, USA
pflood@stanford.edu

Rik Gosselink
Faculty of Movement and Rehabilitation Sciences, Department Rehabilitation Sciences, KU Leuven
Leuven, Belgium

Division of Respiratory Rehabilitation
University Hospitals Leuven
Leuven, Belgium

Division of Critical Care Medicine
University Hospitals Leuven
Leuven, Belgium
rik.gosselink@kuleuven.be

David M. Griffith
University of Edinburgh
Edinburgh, UK

NHS Lothian, Edinburgh, UK
David.M.Griffith@ed.ac.uk

D. Grimaldi
Department of Intensive Care
CUB-Erasme, Université Libre de Bruxelles (ULB)
Brussels, Belgium
David.Grimaldi@erasme.ulb.ac.be

Julius J. Grunow
Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK)
Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
julius.grunow@charite.de

Greet Hermans
Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven
Leuven, Belgium

Department of General Internal Medicine
Medical Intensive Care Unit
University Hospitals Leuven
Leuven, Belgium
greet.hermans@uz.kuleuven.be

Margaret Herridge
Interdepartmental Division of Critical Care Medicine, University of Toronto
Toronto, ON, Canada

Respiratory and CCM, Toronto General Hospital
University of Toronto
Toronto, ON, Canada

Toronto General Research Institute
University of Toronto
Toronto, ON, Canada

Institute of Medical Sciences
University of Toronto
Toronto, ON, Canada
margaret.herridge@uhn.ca

Theodore J. Iwashyna
Department of Internal Medicine
University of Michigan
Ann Arbor, MI, USA

Veterans Affairs Center for Clinical Management Research, HSR&D Center for Excellence
Ann Arbor, MI, USA

Institute for Social Research
Ann Arbor, MI, USA
tiwashyn@umich.edu

Samir Jaber
DAR B, Saint Eloi University Hospital and Montpellier University, INSERM U1046
Montpellier, France
s-jaber@chu-montpellier.fr

James C. Jackson
Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, TN, USA

Geriatric Research Education and Clinical Center, VA Tennessee Valley Healthcare System
Nashville, TN, USA
james.c.jackson@vanderbilt.edu

Boris Jung
Medical Intensive Care Unit
Lapeyronie University Hospital and Montpellier University, INSERM U1046
Montpellier, France
b-jung@chu-montpellier.fr

Jennifer E. Jutte
Wellness and Rehabilitation Psychological Services
Seattle, WA, USA
jensphd@gmail.com

Nancy Kentish
Critical Care Department, St-Louis Hospital, ECSTRA Team, and Clinical Epidemiology, UMR 1153 (Center of Epidemiology and Biostatistics Sorbonne Paris Cité, CRESS), INSERM, Paris Diderot Sorbonne University, Paris, France

Famiréa Research Group
Saint Louis Hospital, AP-HP
Paris, France
nancy.kentish@aphp.fr

D. Langer
Faculty of Movement and Rehabilitation Sciences, Department Rehabilitation Sciences, KU Leuven
Leuven, Belgium

Division of Respiratory Rehabilitation
University Hospitals Leuven
Leuven, Belgium
daniel.langer@kuleuven.be

Caroline Lassen-Greene
Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, TN, USA

Geriatric Research Education and Clinical Center, VA Tennessee Valley Healthcare System
Nashville, TN, USA
caroline.lassen-greene@vanderbilt.edu

Nicola Latronico
Department of Medical and Surgical Specialties Radiological Sciences and Public Health
University of Brescia
Brescia, Italy

Department of Anesthesia, Intensive Care, and Emergency, Spedali Civili University Hospital
Brescia, Italy
nicola.latronico@unibs.it

Thomas Lescot
Surgical Intensive Care Unit
Saint Antoine Hospital
Paris, France
thomas.lescot@aphp.fr

Wilhelmus G. P. M. Looijaard
Department of Intensive Care Medicine
VU University Medical Center Amsterdam
Amsterdam, The Netherlands

Department of Nutrition and Dietetics
Internal Medicine, VU University
Medical Center Amsterdam
Amsterdam, The Netherlands
w.looijaard@vumc.nl

Pablo Lucas Massanet
Intensive Care Unit, Nimes University Hospital
Nimes, France
pablo.lucas.MASSANET@chu-nimes.fr

Stefan Matecki
Department of Physiology, INSERM U1046
Montpellier University
Montpellier, France
s-matecki@chu-montpellier.fr

Robert Memelink
Department of Nutrition and Dietetics
Faculty of Sports and Nutrition
Amsterdam University of Applied Science
Amsterdam, The Netherlands
r.g.memelink@hva.nl

Judith L. Merriweather
University of Edinburgh
Edinburgh, UK

NHS Lothian, Edinburgh, UK
judith.merriweather@ed.ac.uk

Jeroen Molinger
Department of Intensive Care Adults, Erasmus MC, University Medical Centre Rotterdam
Rotterdam, The Netherlands

BeLife Clinical Human Performance Lab
Rotterdam, The Netherlands
j.molinger@erasmusmc.nl

David Orlikowski
Intensive care unit, CIC INSERM 1429
Raymond Poincaré Hospital
Garches, France
david.orlikowski@aphp.fr

Heleen M. Oudemans-van Straaten
Department of Intensive Care Medicine
VU University Medical Center Amsterdam
Amsterdam, The Netherlands

Institute for Cardiovascular Research
VU University Medical Center Amsterdam
Amsterdam, The Netherlands
h.oudemans@vumc.nl

F. Pène
Service de Médecine Intensive – Réanimation
hôpital Cochin, Hôpitaux Universitaires Paris Centre, Assistance Publique – Hôpitaux de Paris
Paris, France

Faculté de Médecine
Université Paris Descartes
Paris, France

Institut Cochin, INSERM U1016, CNRS UMR8104
Paris, France
frederic.pene@aphp.fr

Jean-Charles Preiser
Department of Intensive Care
Erasme Hospital, Université libre de Bruxelles
Brussels, Belgium
jean-charles.preiser@erasme.ulb.ac.be

Danielle Heloisa Prevedello
Department of Intensive Care
Erasme University Hospital
Université libre de Bruxelles
Brussels, Belgium
Danielle.Prevedello@erasme.ulb.ac.be

Zudin Puthucheary
William Harvey Research Institute
Queen Mary University
London, UK
z.puthucheary@qmul.ac.uk

Bara Ricou
Department of Acute Medicine
Université de Genève
Geneva, Switzerland
bara.ricou@hcuge.ch

J. J. Schlesinger
Vanderbilt University Medical Center
Nashville, TN, USA
joseph.j.schlesinger@Vanderbilt.Edu

Lavarnan Sivanathan
Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health
University of Toronto
Toronto, ON, Canada

Department of Anesthesia
University of Toronto
Toronto, ON, Canada
l.sivanathan@mail.utoronto.ca

Yoanna Skrobik
McGill University
Montreal, QC, Canada
yoanna.skrobik@mcgill.ca

Virginie Souppart
Famiréa Research Group
Saint Louis Hospital, AP-HP
Paris, France
virginie.souppart@aphp.fr

Sandra N. Stapel
Department of Intensive Care Medicine
VU University Medical Center Amsterdam
Amsterdam, The Netherlands
s.stapel@vumc.nl

Kristina Stepanovic
Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, TN, USA
kristina.n.stepanovic@vanderbilt.edu

Nathalie Van Aerde
Laboratory of Intensive Care Medicine
Department of Cellular and Molecular Medicine, KU Leuven
Leuven, Belgium
nathalie.vanaerde@kuleuven.be

Greet Van den Berghe
Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven
Leuven, Belgium
greet.vandenberghe@kuleuven.be

Lisa Van Dyck
Laboratory of Intensive Care Medicine
Department of Cellular and Molecular Medicine, KU Leuven
Leuven, Belgium
lisa.vandyck@kuleuven.be

M. Van Hollebeke
Faculty of Movement and Rehabilitation Sciences, Department Rehabilitation Sciences, KU Leuven
Leuven, Belgium

Division of Critical Care Medicine
University Hospitals Leuven
Leuven, Belgium
marine.vanhollebeke@kuleuven.be

Ilse Vanhorebeek
Laboratory of Intensive Care Medicine
Department of Cellular and Molecular Medicine, KU Leuven
Leuven, Belgium
ilse.vanhorebeek@kuleuven.be

Elizabeth M. Viglianti
Department of Internal Medicine
University of Michigan
Ann Arbor, MI, USA
eviglian@med.umich.edu

Bharath Kumar Tirupakuzhi Vijayaraghavan
Division of Critical Care
Apollo Hospitals, Chennai & the Chennai Critical Care Consultants Group
Chennai, TN, India
bharathkumartv@gmail.com

Carl Waldmann
ICU Royal Berkshire Hospital
Reading, UK
cswald@aol.com

Timothy S. Walsh
University of Edinburgh
Edinburgh, UK

NHS Lothian
Edinburgh, UK

Department of Anaesthesia
Critical Care & Pain Medicine
Royal Infirmary of Edinburgh
Edinburgh, UK
timothy.walsh@ed.ac.uk

Steffen Weber-Carstens
Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK)
Charité – Universitätsmedizin Berlin
corporate member of Freie Universität Berlin
Humboldt Universität zu Berlin and Berlin Institute of Health
Berlin, Germany

Berlin Institute of Health, Berlin (BIH)
Berlin, Germany
steffen.weber-carstens@charite.de

Peter J. M. Weijs
Department of Intensive Care Medicine
VU University Medical Center Amsterdam
Amsterdam, The Netherlands

Department of Nutrition and Dietetics
Internal Medicine, VU University Medical Center Amsterdam
Amsterdam, The Netherlands

Department of Nutrition and Dietetics
Faculty of Sports and Nutrition
Amsterdam University of Applied Science
Amsterdam, The Netherlands

Amsterdam Public Health research institute
VU University Medical Center Amsterdam
Amsterdam, The Netherlands
p.weijs@vumc.nl

X. Willaert
Ziekenhuis Oost-Limburg
Genk, Belgium
xavierwillaert@gmail.com

Tobias Wollersheim
Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK)
Charité – Universitätsmedizin Berlin
corporate member of Freie Universität Berlin
Humboldt Universität zu Berlin and Berlin Institute of Health
Berlin, Germany

Berlin Institute of Health, Berlin (BIH)
Berlin, Germany
tobias.wollersheim@charite.de

Hannah Wunsch
Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health
University of Toronto
Toronto, ON, Canada

Department of Anesthesia
University of Toronto
Toronto, ON, Canada

Department of Critical Care Medicine
Sunnybrook Health Sciences Centre
Toronto, ON, Canada

Interdepartmental Division of Critical Care Medicine, University of Toronto
Toronto, ON, Canada
hannah.wunsch@sunnybrook.ca

Introduction

Contents

The Post-ICU Syndrome, History and Definition

Hans Flaatten and Carl Waldmann

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_1

1

Learning Objectives

- The gradual shift in outcome objectives from pure survival to include also a variety of quality of life indicators in survivors during the last 30 years.
- Non-survival outcomes are plural and can be divided in physical, cognitive and mental morbidity.
- The common term post-ICU syndrome emerged in 2010 and includes all morbidity with roots in a former ICU admission and includes to some extent also caregivers.
- The post-ICU syndrome is frequently documented in former ICU patients.

1.1 Introduction

There is more to life than measuring death.

Intensive care or critical care is historically a young branch on the medical tree. In Europe, most will consider the start to be during the large Polio epidemics in Northern Europe the beginning of the 1950s. The year 1952 particularly witnessed large outbreaks with a very high mortality rate because of a high rate of bulbar affections. This was accompanied by a high mortality, also in the very young polio patients. The birth of intensive care is by many considered to be August 26, 1952. The Danish anaesthesiologist Bjørn Ibsen demonstrated that his knowledge and skills, specifically with airway management, ventilation and fluid therapy, rescued a young 12-year-old girl from a certain death caused by respiratory failure [1]. Her name was Vivi, and her post-ICU trajectory is very well documented including some evidence of her quality of life (see ▶ Box 1.1) [2].

Also, in the USA, care of the critically ill patients developed, and Peter Safar and Max Weill pioneered and developed intensive care further.

This chapter will describe the history and development of the various outcome methods and research usually applied in intensive care, all leading to the current understanding and definition of what we today call the post-ICU syndrome (PICS). ◘ Figure 1.1 gives a rough overview of the timeline from 1950 with important years for events that will be described more detailed in the text, and in the end PICS will be described and defined.

Box 1.1: The life of Vivi After Intensive Care (Translated from B. Ibsen's Own Hand-written Records [2])

Until January 1953 she was manually ventilated 24/7. There followed a very lengthy recovery. Again and again she developed atelectasis that was treated with bronchoscopy and antibiotics. She was still dependent on artificial ventilation. Over the following years, different models of respirators were tried. The technology improved as new models were developed. It was not until 1955 that a respirator entered the market which could support ventilation satisfactorily. Only by then, the manual positive pressure ventilation was no longer necessary at intervals. Vivi E. remained, according to the record, dependent on artificial ventilation for the rest of her life.

When she was released From Blegdams Hospital in 1959 (!), she was bound to a wheelchair because of quadriplegia. She could speak, and scroll through a book with a stick in her mouth, but needed help for eating and the daily nursing. Vivi's mother was trained in the use of the respirator and Vivi was released to her own home where she lived with her parents. In June 1971 she was again admitted to the Blegdams Hospital with diabetes and a severe pneumonia. She died after 2½ days in the hospital from pneumococcal sepsis.

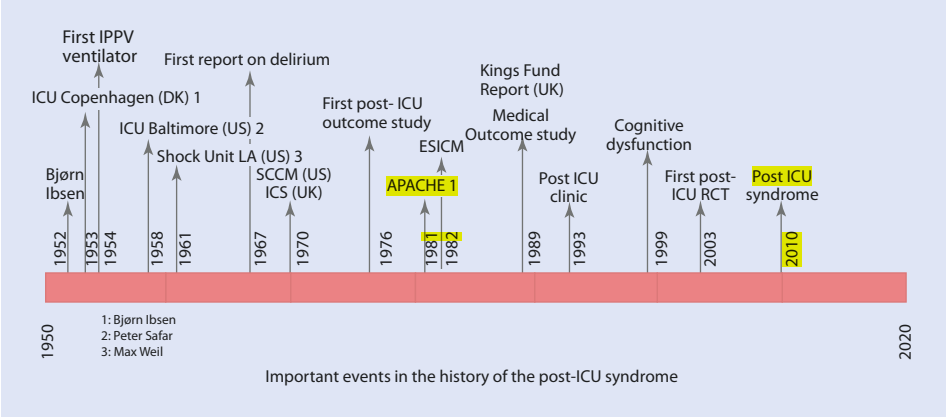


Fig. 1.1 Timeline from Bjørn Ibsen until today

1.2 In the Beginning, There Was Survival and Death

For the next two decades, intensive care was mainly concerned about getting the patients to survive their critical illness, and hence the clinical scope was either ICU or hospital survival. In parallel there was a rapid development of equipment, necessary to get more patients to survive when their vital organs failed. The development of ventilators to replace the manual ventilation performed in 1952, was rapid, and most often intensive care was synonymous with patients on mechanical ventilation. Hence, outcome was usually considered equal to survival in the intensive care, an attitude that later was reinforced by the first severity of disease scoring systems like APACHE and SAPS were the probability of survival could be estimated.

Little was written, at least in the medical literature, about the fate of survivors from intensive care, but that was to change.

1.3 The Shift in Focus on Post-ICU Outcomes

Possibly one of the first outcome papers to include a follow-up of ICU survivors during the first year after ICU discharge was a special article in NEJM in 1976 [3]. The title "Survival, hospitalization charges and follow-up results in critically ill patients" clearly demonstrates a different approach to intensive care. Not only survival but also costs and non-mortality outcomes were addressed. Patients followed a subset of admission to a recovery room, acute care unit at Harvard Medical School in 1972–1973. Of the 226 patients in need of intensive physician and nursing care, 27% survived the first year. After discharge, the patients were followed up at 3, 6 and 12 months. This was done by a visit to the hospital, by telephone or by mail. They gave direct questions about the extent of recovery, mental status, functional status and current patient locations. At 12 months, most of the remaining survivors (62) were at home, but 11 were still in the hospital! They observed the mental function to recover more quickly than physical capacity, an interesting discovery that also have been observed later [4]. Forty-two per cent (26) of the one-year survivors had the same functional level as before the critical illness, and 10 (16%) were in a nursing home. The overall outcome from 1 to 12 months is summarised in Fig. 1.2.

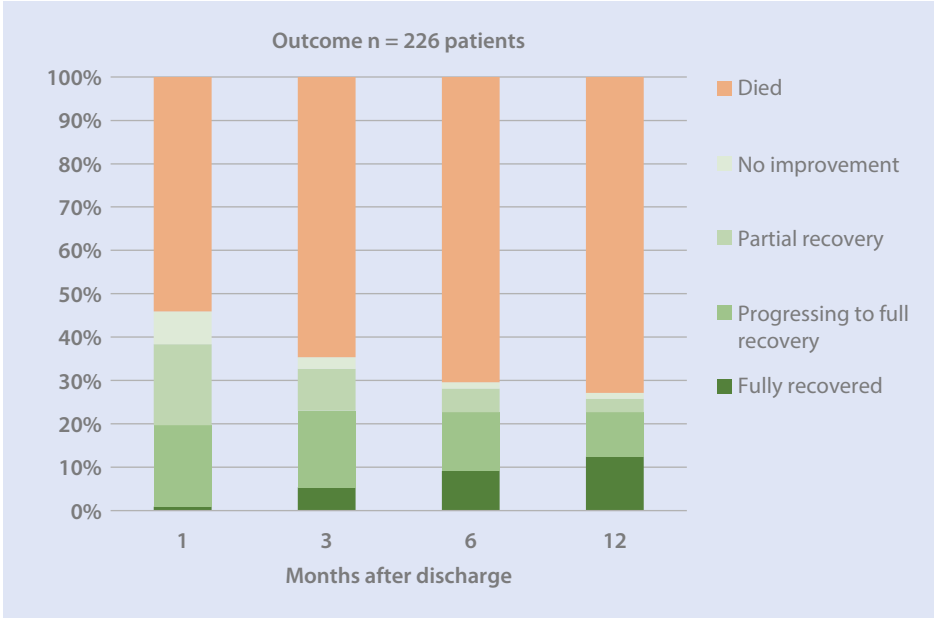


Fig. 1.2 Outcome first year [4]

They also demonstrated a profound negative effect on survival in the old (≥65 years) compared to younger, but they had the same profile in their non-mortality outcomes.

In this first comprehensive analysis using a broader approach to outcomes, many of the features we observe today in our ICU survivors were in fact described!

However, this was a "lonely rider" among intensive care publications, and active research and clinical reports from the post-ICU period were still infrequent.

In the mid-1980s, more systematic follow-up of the ICU survivors started in Liverpool, UK, by Richard Griffiths [5]. Their experience resulted in a request from the King Fund Panel in 1988 to highlight the needs of ICU survivors. This initiative resulted in the first UK comprehensive study of cost and 6-month mortality and morbidity outcomes from adult intensive care. The study revealed significant amount of post-ICU morbidity both physical and psychological which in turn led to restriction in activities of daily life or disability in many patients [6]. Later, the report from the King Fund Panel advocated that non-mortality outcomes should regularly be reported in ICU survivors [7], a request that later was followed up by the National Health Service (NHS) in the UK.

In 1993, following the Liverpool experience, a dedicated ICU follow-up clinic was set up in the UK and was one of the first in Europe. The clinic was set up in Reading and was named Intensive After Care After Intensive Care. The clinic was run jointly by an ICU nurse and an ICU consultant twice a month, and its costs were estimated at 1% of the ICU budget [8] (REF).

1.4 Health-Related Quality of Life (HRQol) Instruments Surveys

Until the late 1980s, HRQol was measured and reported in a non-standardised way, making comparison between different studies difficult. Unlike the easy way of defining and measuring death, HRQol was a more much more complex and composite outcome mea-

sure. The emerging interest of non-mortality outcome in intensive care was doubtless influenced by similar activity towards other patient populations. Clinical research aimed to describe the outcome of patients was increasingly engaged in documenting non-mortality outcomes, in particular in groups with a low mortality where non-mortality outcomes were more relevant. One of the most successful initiatives was the Medical Outcomes Study and the development of Short Form 36 (SF-36) in 1989 [9]. This is a generic HRQol questionnaire with 36 items and 8 domains and has been proven valuable in many disease conditions. The questionnaire was also used in ICU survivors, first known publication that appeared in BJA in 1995 [10], and has later been one of the more popular instruments also in the post-ICU population, although its complexity makes it not ideal for self-completion.

Another initiative worth mentioning is the EuroQol development. The work with this generic quality of life instrument started in 1987 with the aim to have a relevant yet simple, generic instrument to describe HRQol, a standardised tool and suitable for self-completion. The group published the first development paper in 1990 [11], but the instrument was further refined after empirical testing and was formally named EQ-5D in 1995. The instrument was identified in 2004 as the preferred instrument for measuring HRQol by NICE in the UK [12]. Lately, it is routinely used today for various patient reported outcome measurement (PROM) programs because of its simplicity.

1.5 Cognitive Decline After Critical Illness

Examination of mental state have been essential in psychiatric patients for decades, and several lengthy assessments were available in the 1970s. In 1975, a faster instrument called the "Mini-Mental State" (MMS) examination was introduced [13]. This is a simplified scored form of cognitive state and is composed of only 11 questions. It is fast and easy to use and is today probably the most used screening methods for cognition as well as in the post-ICU setting. However, it reveals no in-depth understanding and mapping of cognitive dysfunction.

Cognition was definitively put on the ICU agenda with the very important research on follow-up in patients with severe ARDS in the late 1990s and was the focus on a paper from the USA in 1999 [14]. In that study, all 55 patients showed cognitive impairment at hospital discharge, and 30% still had general cognitive decline at 1 year follow-up. More than 3 out of 4 had one either impaired memory, attention, concentration or decreased mental speed. A link to long periods of desaturation during the mechanical ventilation and hence a neurocognitive effect of hypoxaemia was a suggested mechanism. Similar results were found in a study from 2006, using a very different approach to cognitive testing using a touch screen computer software (Cantab) enabling testing when still in the ICU and follow through the post-ICU period [15].

A problem with studies on cognition is the very different methods used, sometimes in a non-standardised way between studies. The traditional method of using specially trained personnel to deliver this test on paper was used in the first study. However, availability of neuropsychologists to perform testing is difficult and resource demanding, and is not available for all. The development of more automated testing using laptops or tablets to present the tests online is a huge step towards standardisation. One such instrument is developed by researchers in Cambridge: the Cambridge Neuropsychological Test Automated Battery (▶ http://www.cambridgecognition.com/) making a low-threshold instrument available for research, even into the ICU (◘ Picture 1.1) [16].

Picture 1.1 CANTAB applied on an ICU patient. This patient is dependent on respiratory support through a tracheostomy. The test is done bedside and accompanied only by the laptop and the investigator

1.6 Physical Impairment

Several forms of physical impairment have been described in patients surviving intensive care. Frequently signs of such impairment have been overt already in the ICU or hospital, but sometimes problems may develop more gradually.

1.6.1 Neuromuscular Dysfunction

First described in 1984 [17] as polyneuropathy in five patients, it has today been better described as polyneuromyopathy, since not only nerves but also the muscles can be involved. Today up to 50% of ICU patients have been described having one of the three forms described [18]. Usually this development is evident in the ICU, and is a frequent cause of slow and difficult weaning from the ventilator, and impairs mobilisation of the patient.

1.6.2 Respiratory Dysfunction

Pulmonary tissues may also be affected directly in several diseases. Most extensively this have been studied in ARDS survivors which was first documented in 1989 [19] when an extensive follow-up of 41 ARDS survivors found pulmonary impairment of 18 of 27 that

could be followed to 1 year. Most, however, suffered from mild impairments. An overview of several prospective studies in this patient group have been published and linked HRQOL with measurements of lung functions [20].

1.6.3 Cardiovascular Dysfunction

Surprisingly, data about cardiovascular failure after discharge from intensive care is difficult to find. However, a study using SOFA during ICU admission revealed that mortality after discharge was highest (OR 2.5) in the group with cardiovascular failure [21].

1.6.4 Renal Dysfunction

In the late 1990s, a more active approach to the treatment of acute kidney injury was established. A particularly high mortality rate was found in these patients, with hospital mortality reported from 50 to 80%. However, first in 2002 one of the first studies with the aim to study post hospital outcomes in AKI patients was published [22]. In that study the in-hospital mortality was high (69%), but in the survivors 50% post-hospital mortality was reached after 5 years with a seemingly good QOL. No data for dependence of dialysis was given. More recent data, however, reveals that AKI is a marker of a poor prognosis, and these patients should be followed closely after discharge [23].

1.7 Post-Intensive Care Syndrome (PICS)

The united name for all chronic disabilities that may appear because of critical illness is usually today named the post-ICU syndrome (PICS). It is important to understand that this is not one singular disease state, and it is not even confined to former ICU patients but also to some extent also to their caregivers. Figure 1.3 adapted from [24] put this into perspective. It is unclear where and when the name PICS appeared but was used in a multidisciplinary conference arranged by the Society of Critical Care Medicine in 2010, which was published in 2012. Since then, PICS has been adopted by the ICU community worldwide as the wide range of problems that often occur post-ICU discharge. There is no official definition of this syndrome which is not listed as a Mesh-term by NCBI nor can it

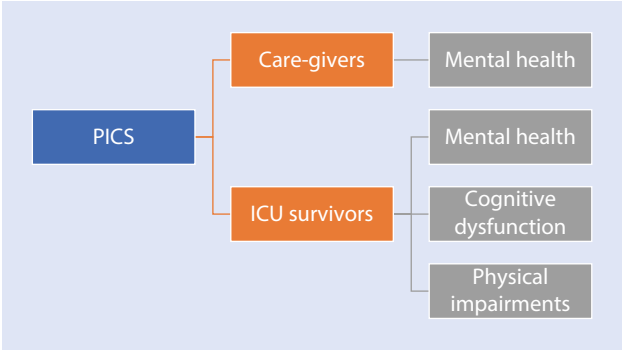


Fig. 1.3 The post-intensive care syndrome

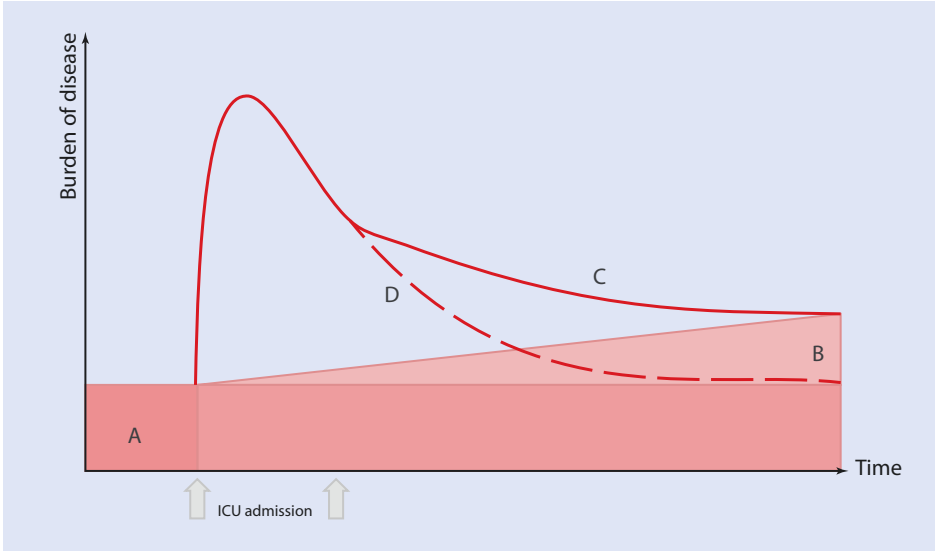


Fig. 1.4 The burden of disease post-ICU. A = pre-ICU burden (co-morbidity), B = possible increase of burden by worsening of A, C = ICU burden not returning to zero, D = ICU burden returning to zero. B and C both represents the development of PICS

be found in the upcoming ICD-11 disease codes to be implemented in 2018. Most will probably agree that the syndrome includes new or aggravated dysfunction(s) in physical domain, cognitive domain and/or mental (psychiatric) domain in the period after critical illness but not confined to a specific disorder (Fig. 1.4).

PICS is probably related to the increased rate of death seen in former ICU patients for many years after discharge, but clear evidence of which elements of the PICS being the most important is at present not revealed.

A specific focus at present is on patient reported outcomes (PROM) as well as after intensive care. From 2009, it has been mandatory for all providers (NHS hospitals, independent sector treatment centres, private hospitals) treating NHS patients for any of four elective procedures to participate in the national PROM programme [25]. The concept has rapidly been taken up by other national health care programs and has also been implemented in post-intensive care setting (Sweden).

1.8 Prevention of PICS

With prevention of PICS, one must deal with the different entities that compose the syndrome. This was on the agenda already in the 1990s when more and more of the burden of disease with origin from intensive care was revealed. Research on treatment and prevention in this context is not extensive and has concentrated on some mental disorders and physical disorders. One of the first randomised trials published was from the UK in 2003 [26]. They found a self-help rehabilitation manual to be effective in physical recovery and reducing depression post-ICU. The use of diaries from the ICU stay has also been shown to reduce post-traumatic stress disorders following critical illness [27]. However, a recent meta-analysis found little evidence for an effect of follow-up consultations in general, and

documented overall low quality of studies are included [28]. A Cochrane review from 2015 of exercise-based intervention following intensive care likewise was unable to determine the overall effect on functional exercise capacity or on HRQOL in ICU survivors [29].

Take-Home Messages

- The concept of post-intensive care burden has developed gradually over 20–30 years with a description of individual disease states that become apparent in patients after discharge from the ICU.
- The common name for this (regardless of the profile of diseases) is now the post-intensive care syndrome (PICS). It may cause significant morbidity and probably also increase the mortality in former ICU patients.
- Until now there are many excellent reports on its occurrence and epidemiology, but less is understood about the factors in play and how we can prevent and treat it.

References

1. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med. 1954;47:72–4.
2. Reisner-Senelar L. The birth of intensive care medicine: Bjørn Ibsens records. Intensive Care Med. 2011;37:1084–6.
3. Cullen DJ, Ferrara L, Briggs B, et al. Survival, hospitalization charges and follow-up results in critically ill patients. NEJM. 1976;294:982–7.
4. Eddlestone JM, White P, Guthrie E. Survival, morbidity and quality of life after discharge from intensive care. Crit Care Med. 2000;28:2293–9.
5. Griffiths RD, Jones C. Seven lessons from 20 years of follow-up of intensive care unit survivors. Curr Opin Crit Care. 2007;13:508–13. https://doi.org/10.1097/MCC.0b013e3282efae05.
6. Shiell AM, Griffiths RD, Short AIK, Spiby J. An evaluation of the costs and outcome of adult intensive care in two units in the UK. Clin Intensive Care. 1990;1:256–62.
7. ICU in the UK: report from the King's Fund Panel. Intensive Care Nurs. 1989;5:76–81.
8. Griffiths J, Gager M, Waldman C. Follow-up after intensive care. Contin Educ Anaesth Crit Care Pain. 2004;4:202–5.
9. Tarlov AR, et al. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. JAMA. 1989;262:925–30.
10. Smith IE, Shneerson JM. A progressive care programme for prolonged ventilatory failure: analysis of outcome. Br J Anaesth. 1995;75:399–404. https://doi.org/10.1093/bja/75.4.399.
11. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990;36:199–208.
12. NICE. Guide to the methods of technology appraisal. London: National Institute for Clinical Excellence; 2004.
13. Folstein M, et al. Mini-mental state, a practical method for grading the cognitive state of patients for clinicians. J Psychiatr Res. 1975;12:189–98.
14. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LO. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160:50–6.
15. Jones C, Griffiths RD, Slater T, Benjamin KS, Wilson S. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. Intensive Care Med. 2006;32:923–6.
16. Torgersen J, Hole J, Wenzel-Larsen T, Flaatten H. Cognitive impairments after critical illness. Acta Anaesthesiol Scand. 2011;55:1044–51.
17. Bolton CF, Gilbert J, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry. 1984;47:1223–31. PMCID: PMC1028091.

18. Shepherd S, Batra A, Lerner DP. Review of critical illness myopathy and neuropathy. Neurohospitalist. 2017;7:41–8. https://doi.org/10.1177/1941874416663279.
19. Andrew J, Ghio AJ, Elliott CG, Crapo RO, Berlin SL, Jensen RL. Impairment after adult respiratory distress syndrome: an evaluation based on American Thoracic Society recommendations. Am Rev Respir Dis. 1989;139:1158–62. https://doi.org/10.1164/ajrccm/139.5.1158.
20. Wilcox E, Herridge M. Lung function and quality of life in survivors of the acute respiratory distress syndrome (ARDS). Presse Med. 2011;40:e595–603. https://doi.org/10.1016/j.lpm.2011.04.024.
21. Lone NI, Walsh TS. Impact of intensive care unit organ failures on mortality during the five years after a critical illness. Am J Respir Crit Care Med. 2012;186:640–7. https://doi.org/10.1164/rccm.201201-0059OC.
22. Morgera S, Kraft A, Siebert G, Luft F, Neumayer HH. Long term outcomes in acute renal failure patients treated with continuous renal replacement therapy. Am J Kidney Dis. 2002;40:275–9.
23. Flaatten H, Darmon M. A nephrologist should be consulted in all cases of acute kidney injury in the ICU: yes. Intensive Care Med. 2017;43:874–6. https://doi.org/10.1007/s00134-017-4790-4.
24. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:502–9. https://doi.org/10.1097/CCM.0b013e318232da75.
25. Black N. Patient reported outcome measures could help transform healthcare. BMJ. 2013;346:f16. https://doi.org/10.1136/bmj.f167.
26. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31:2456–61.
27. Jones C, Bäckman C, Capuzzo M, Egerod I, Flaatten H, Granja C, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. Crit Care. 2010;14:R168. https://doi.org/10.1186/cc9260.
28. Jensen JF, et al. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41:763–75. https://doi.org/10.1007/s00134-015-3689-1.
29. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, MPW G, Hart N, Walsh TS, Blackwood B, ERACIP Group. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev. 2016;7(5):520–6. Epub 2016 Sep 16. https://doi.org/10.1002/jcsm.12146.

The Differential Diagnosis of Persistent Critical Illness and Other Causes of Prolonged ICU Stays

Theodore J. Iwashyna and Elizabeth M. Viglianti

This is based on a manuscript first published by Iwashyna TJ and Viglianti EM. Patient and population-level approaches to persistent critical illness and prolonged intensive care unit stays. Crit Care Clin. 2018;34(4):493–500. ► https://doi.org/10.1016/j.ccc.2018.06.001. PubMed PMID: 30223989; PMCID: PMC6146412.

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_2

2

Learning Objectives

- Provide an approach to understanding why patients develop prolonged ICU stays (>10 days), dividing causes into intrinsic patient characteristics, things that happen in the ICU, and organizational failure.
- Define the concept of persistent critical illness, as those patients whose "reason for being in ICU is now more related to their ongoing critical illness than their original reason for admission to the ICU."
- Clarify how persistent critical illness is conceptually related to but not identical to the concepts of chronic critical illness and prolonged mechanical ventilation.
- Summarize existing empirical data on the population-level drivers of prolonged ICU stay, arguing that the data are most consistent with persistent critical illness being the most common cause in several different health systems.

Consider taking over a clinical service in an ICU. As you receive handoff of the patients, you are told it is ICU day 11 for the patient in bed 06. What differential diagnosis will allow you to appropriately move forward with this patient? We suggest Table 2.1 as one approach to the differential for such a patient. Broadly, this differential diagnosis can be organized into 3 categories:

- Intrinsic patient and admitting diagnostic characteristics
- Things that happen during the course of critical illness
- System failures

In this chapter, we will develop an approach to patients with prolonged ICU stays. First, we will briefly sketch the system issues that make these rare patients—those with an ICU stay of more than 10 days—worthy of consideration. Second, we will consider the patient-level differential diagnosis of these patients, surveying the explanations that have been proffered for them. Third, we will review the existing epidemiologic evidence asking: at a population level, what can we say about the relative commonness of the various individual-level processes to generate the system issues? Finally, we will speculate—and we want to be clear, these will be frank speculations—on the potential clinical and research implications of this line of work.

2.1 The Epidemiology of Long Stays in the ICU

Prolonged intensive care unit (ICU) stays while not common are costly, increasing in prevalence, and results in long-term morbidity [1–3]. In 2009, in the United States, it was estimated that 380,000 cases remained in the ICU for at least 8 days with an estimated $25 billion in hospital-related costs [1]. With an aging population and advancements in critical care, more people are surviving their admitting diagnosis only to remain in the intensive care unit for prolonged periods of time being subjected to the complications and problems which can occur while being hospitalized [4]. However, once the patient is discharged, the sequelae of the problems from the prolonged ICU hospitalization continue to impact the patient and their caregivers. The mortality is higher than most malignancies in the subsequent year (48–73%) [3, 5]. Of those who survive, many have functional and cognitive disabilities [3, 6]. Only 20% are discharged directly home from their prolonged ICU stay, with the majority being discharged to long-term acute care facilities (LTACs) or subacute care rehabilitation (SAR) facilities [5].

Table 2.1 Differential diagnosis of patients with prolonged ICU stays

Differential diagnosis	Testable implications in existing data
Intrinsic patient characteristics	
Diseases with long intrinsic recovery time Neurologic Pulmonary Inflammatory Complex nursing needs	Long stayers concentrated in a few discrete diagnoses
Frailty	Very high mortality, older age, more comorbidity (all present on admission) predictive of persistent critical illness
Acute unrecoverable illness	Very high mortality
Things that happen in the ICU	
Acquired single-organ problems	
Failure to wean from ventilator/muscle & diaphragmatic weakness/prolonged mechanical ventilation	Long stayers mostly ventilated, predominantly hypercarbic respiratory failure
Van den Beghe endocrinopathy	Unclear population-level implications
Malnutrition/protein wasting	Unclear population-level implications
Dynamic cascades in multiple organs	
Cascading critical illness	Increasing irrelevance of admitting diagnosis to prognosis with longer time in ICU
Cascade iatrogenesis	Increasing irrelevance of admitting diagnosis to prognosis, *plus* measureable errors
Immunoparalysis	Predominance of sepsis among later organ failures
Organizational Failures	
Bedblock	Little difference in mortality
Admitting patients with unrealistic expectations or lack of palliative care involvement	Very high mortality
Idiosyncratic requirements for ICU care for certain types of care	Little difference in mortality

Diverse definitions of "prolonged" have been used across studies. A meta-analysis of 124 studies with prolonged mechanical ventilation provides an illustrative example. Inclusion criteria for studies were "(1) mechanical ventilation for 14 days or more, (2) mechanical ventilation with admission to a specialized ventilator weaning unit in either an acute care hospital or a post-acute care hospital, or (3) mechanical ventilation for 96 hours or more plus a tracheostomy procedure (i.e., diagnosis-related group [DRG] for tracheostomy for acute respiratory failure)" [5]. In general, these definitions of "prolonged" have been based on an expert opinion and/or the exigencies of data availability.

Despite these variations in important details of the definition, a coherent picture emerges: there are a modest number of patients who nonetheless require vast resources. The math of prolonged ICU stays is ineluctable—the number of bed-days required by these patients will be at least an order magnitude higher than the number of patients. Providers' experiences and hospital systems' budgets are driven by the number of bed-days.

As an example, Iwashyna et al. used a population-based and statistical definition to identify a group of patients with prolonged ICU length of stay which they termed "persistent critical illness" [7]. Such persistent critical illness patients accounted for only 5.0% of all ICU patients in Australia and New Zealand—yet also 32.8% of all ICU bed-days and 14.6% of all hospital bed-days by ICU patients. Using the same definition, Bagshaw et al. found that such patients accounted for 16.1% of all ICU patients in Alberta, Canada—yet also 54.5% of ICU bed-days and 36.3% of hospital bed-days by ICU patients [8].

2.2 Patient-Level Differential Diagnosis

Given the generality of the motivating problem—a "long" stay in the ICU—there will not be a single cause for all such patients. As such, a broad differential diagnosis must be considered (Table 2.1).

2.2.1 Intrinsic Patient and Admitting Diagnostic Characteristics

The most obvious reason for a patient to have a long stay in the ICU is that there are some admitting diagnoses that (a) take a long time from which to recover, (b) are not highly lethal if provided contemporary supportive care, and (c) for which we lack efficacious therapies. Common diseases with a long intrinsic recovery time include:

- Neurologic disorders: Guillain-Barré and other acute paralysis, myasthenia gravis, traumatic brain injury, certain encephalitides, and acute demyelinating conditions
- Pulmonary: COPD exacerbations in patients with baseline poor lung function, acute exacerbations of interstitial lung disease
- Inflammatory: severe acute pancreatitis, undrainable infections (e.g., pulmonary abscess)
- Complex nursing needs: burns and complex wound care, prolonged withdrawal syndromes
- Patients with unrecoverable illness: whether chronically from frailty or decompensated cirrhosis or acutely, as from a relapsed hematologic malignancy despite multiple transplant attempts

2.2.2 Things that Happen During the Course of Critical Illness

Professor Louise Rose at the American Thoracic Society in 2018 articulated a useful distinction between two different *ICU-acquired* mechanisms which could lead to prolonged ICU stays: (1) chronic critical illness, where patients "experience relative clinical stability

but continue to require prolonged ICU stay and (usually) prolonged mechanical ventilation," and (2) persistent critical illness, which, she said, is "reflected by ongoing critical illness and some degree of instability that is no longer directly attributable to [the patient's] original reason for ICU admission."

As Prof. Rose identified, within chronic critical illness, a major focus of attention has been prolonged mechanical ventilation [5]. This is most commonly attributed to muscle weakness and diaphragmatic failure, leading to hypercarbic respiratory failure—although the empirical basis for such attribution may be weak. More recently, the role of persistent delirium in limiting weaning from mechanical ventilation has received attention. Nelson et al.'s influential work on chronic critical illness placed prolonged mechanical ventilation at the center of its definition [3].

Others have emphasized distinctive pathways into chronic critical illness [9]. Van den Berge's work in the 1990s suggested a potentially important role for an acquired endocrinopathy [10]. Others have hypothesized poor attention to the early nutritional needs of ICU patients as a driver of—not just consequence of—prolonged ICU stays. The effector arms of such iatrogenic malnutrition may be hypothesized to be poor protein intake [11].

A contrasting possibility is that patients in the ICU are not dominated by a single fixed lesion, either present on admission or acquired shortly thereafter. Instead, there are patients with seemingly new problems every day. Patients with persistent critical illness have been defined as those patients whose "reason for being in ICU is now more related to their ongoing critical illness than their original reason for admission to the ICU." A survey of Australian and New Zealand critical care practitioners suggested that such patients were common in their ICUs and were a source of substantial stress to such clinicians [12]. It is possible that such cascading critical illness could be caused by repeated new insults and injuries from the lack of homeostasis, from simple bad luck, or that such cascades could be caused by repeated errors or poor judgment by the care teams—what Hofer et al. have termed "cascade iatrogenesis" [13]. A growing body of work suggests that immune suppression (or "immunoparalysis") is common after sepsis, trauma, and other severe illnesses, and this work implies a causal role for such immune dysfunction in patients stuck in the ICU by placing the patient at risk for the development of new sepsis [14].

2.2.3 Organizational Failures

A third class of reasons for patients to have long stays in the ICU are frank organizational failures. For example, one reason for patients to have prolonged stays in the ICU is that the system lacks the ability to move them out of the ICU once their critical illness is resolved. The incidence of such "bed block" varies across systems and in its duration. Nonetheless, patients who are merely boarding in an ICU awaiting the availability of lower intensity care should be usefully distinguished from those truly still needing the high-level nursing and physician care that define the ICU. Such differentiation rarely presents a challenge for the bedside clinician—but such patients can be difficult to differentiate for the epidemiologist and health services researcher.

The provision of ICU care to patients with unrealistic expectations is a second form of system failure. The general problem is that there are patients who will die regardless of the care they receive. There are systems that routinely fail to detect patients who have no realistic chance of surviving critical illness despite best care and offer such patients ICU care under illusions about its potential benefit. ICU efforts directed to an outcome that

ICU cannot achieve will mandate prolonged periods of time in the ICU. In contrast, some patients may be admitted to the ICU for high-intensity palliative care, in the absence of formal units specializing in acute care of the dying. It is our opinion that such high-intensity palliative care is an entirely appropriate use of ICU, although we suspect such high-intensity palliation rarely is necessary for longer than a week.

A type of organizational failure is caused by hospital policies that mandate the provision of certain therapies in an ICU setting when such care can be safely provided in the ward settings. For example, the authors have worked in hospitals that would only allow use of noninvasive ventilation on the wards in patients who had undergone an outpatient sleep study. As such, all other noninvasive ventilation is needed to be provided in the ICU setting. Differentiating such patients from the persistently critically ill rarely presents a challenge for the bedside clinician.

2.3 Single-Center Evidence on Evolution of Long Stays

There are three detailed single-center studies of patients with prolonged ICU lengths of stay. Viglianti et al. examined 50 consecutive patients who spent at least 14 days in the ICUs of the University of Michigan Medical Center [15]. Jeffcote et al. examined 100 patients who spent at least 10 days in the ICU of the Austin Hospital (Melbourne, Australia), and 100 age, sex, acute physiology and chronic health evaluation (APACHE III) score, and Charlson comorbidity score matched controls [16]. Darvall et al. examined 72 adult patients admitted to the ICU and who spent more than 10 days in the ICU of the Royal Melbourne Hospital, matched on diagnostic code, gender, age within 10%, and acute physiology and chronic health evaluation (APACHE) III risk of death within 10% [17].

In all of the detailed single-site studies, there were surprisingly high rates of successful extubation among patients who remained in the ICU for prolonged periods of time. In the United States, this might be attributed to selective referral of patients with simple prolonged mechanical ventilation to long-term acute care hospitals—although Viglianti et al. argue against this as a major source of bias. Australia has no such long-term acute care hospitals but showed similarly high rates of successful extubation but continued ICU use. Furthermore, among those patients in the Viglianti series who were still intubated after 14, the vast majority remained hypoxic—defined as a PaO_2/FiO_2 ratio of 200 or less—arguing further against simple muscle weakness as the major driver of prolonged mechanical ventilation (see Fig. 2.1).

Taken together, these single-center data suggest that prolonged mechanical ventilation is not the dominant cause of prolonged ICU stays. Instead, extubations may be common, and many continuing intubations or reintubations appear to be caused by extrapulmonary organ failures rather than primary respiratory drivers.

2.4 Population Impact

One might imagine a vast longitudinal cohort study, where patients are assessed in standardized ways by omniscient, highly reliable experts. On each day, each patient's reason for being in the ICU is unambiguously arbitrated into one of a series of mutually exclusive categories. In the context of such an all-seeing apparatus, one might readily count the contribution of each of the aspects of Table 2.1 to the total population burden of prolonged ICU use.

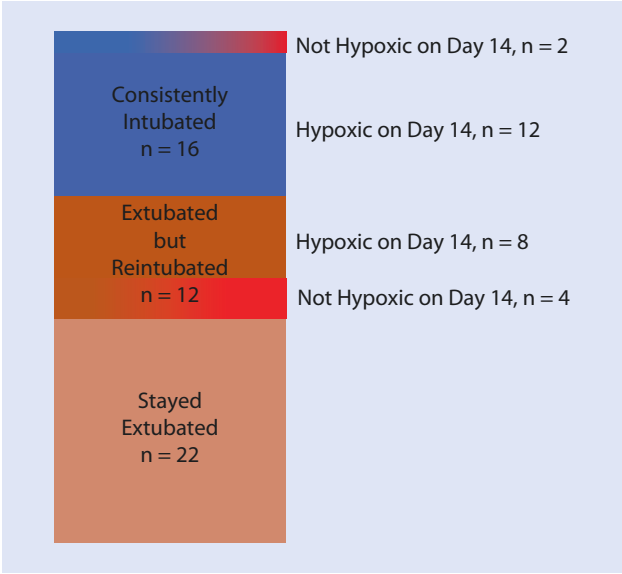


Fig. 2.1 Patterns of respiratory failure in 50 consecutive patients with persistent critical illness. (From Viglianti et al. [15]). Of the 50 patients, 16 were consistently intubated for the first 14 days of their ICU stay (including via tracheostomy), 12 were extubated but reintubated (typically several days later), and 22 were extubated and stayed extubated. Of those 28 still intubated on Day 14, most patients remained hypoxic (PaO_2/FiO_2 < 200), contrary to the hypothesis that they would primarily be hypercarbic ventilator failures from deconditioning. Only 6 of the 50 were intubated but not hypoxic after 14 days

Neither such a vast cohort study nor such omniscient coders exist.

As such, we must consider existing fragmentary data. In 2016, Iwashyna and colleagues examined 1,028,235 critically ill patients from 182 ICUs across Australia and New Zealand, hospitalized from 2000 to 2014. Consistent with Rose's definition, they defined persistent critical illness as occurring when a patient's "reason for being in ICU is now more related to their ongoing critical illness than their original reason for admission to the ICU." They argue that "among patients still alive and in an ICU, onset of persistent critical illness can be empirically identified as the day during critical illness beyond which admission diagnosis and physiological illness severity cease to predict outcome more accurately than do simple antecedent patient characteristics." That is, this cascade of new critical problems would erase the prognostic content of the original diagnosis and admission physiology. In contrast, if persistent critical illnesses were rare and stable chronic critical illnesses were the dominant factor, then, they argued, differences between patients' outcomes would remain based on their admission diagnosis. Bagshaw et al. conducted parallel and independent analyses on the 17,783 patients admitted to 12 ICUs from Alberta, Canada, between June 2012 and December 2014.

In both cases, it was found that at approximately after 10 days in the ICU (after 10 in Australia and New Zealand; after 9 in Alberta), the hypothesized population-level transition of persistent critical illness occurred (see Fig. 2.2). This suggests that for most patients still in the ICU, sometime during the first 2 weeks, new dynamic cascades become the major driver of patients stays. In both systems, these patients account for enormous numbers of ICU bed-days. These core population-based findings have been replicated in analyses—unpublished as of the time of this writing but presented at the 2017 American Thoracic Society International Conference [18]—from both the Veterans Affairs system of 120 hospitals in the United States and in a Scotland-wide database.

Supporting the argument that these prolonged stays are driven by new cascades, Viglianti has shown with colleagues in two different systems that it is very difficult to

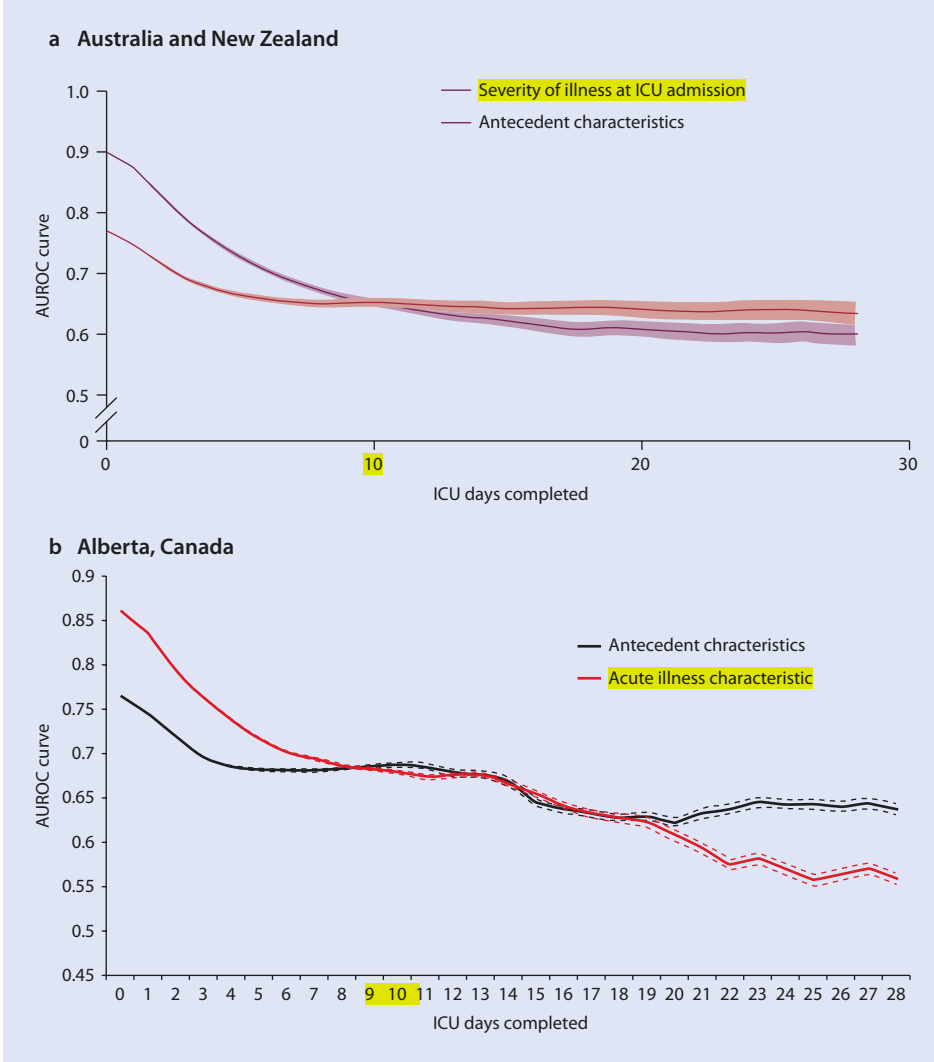


Fig. 2.2 Parallel crossovers in Australia, New Zealand, and Alberta, Canada. Predictiveness of diagnosis and severity of illness at ICU admission as compared to antecedent characteristics for hospital mortality. Shaded areas are 95% confidence intervals. (From Iwashyna et al. [7] and Bagshaw et al. [8]). **a** Australia and New Zealand. **b** Alberta, Canada

predict at admission which patients will develop persistent critical illness [15, 19]. She has further shown that potentially hypothesized predictors, e.g., age and comorbidity, are not in face particularly predictive.

Further supporting this "new cascading events" interpretation are several items from the hospital case series. Viglianti showed that only 22% of patients did *not* develop a new organ failure on day 4 or later—and the median patient experienced 2 new organ failures between days 4 and 14. Darvall used structured criteria to define why the patient was still in the ICU; they report that the original illness was no longer a cause for continued ICU stay after a median (IQR) of 10 (7–16) days.

These data show that across multiple systems, the broad timing of onset of persistent critical illness is similar; yet they also suggest that there is system-level variation in incidence and survival of patients with persistent critical illness. This variation strongly suggests that the incidence of persistent critical illness can be influenced by care practices—although it is not yet known which. Further, it is not known to which extent the higher incidence of persistent critical illness might be termed a "winner's curse," the result of high-quality critical care that saves more people, some of them imperfectly. Alternatively, persistent critical illness might be the result of poor-quality critical care, from incomplete initial resuscitations to recurrent iatrogenic events; such questions are urgently in need of answer.

2.5 Other Observations Regarding Drivers of Prolonged ICU Stays

Population data argue against organizational failure alone as a major reason for prolonged ICU stays. In particular, if the major reasons for prolonged ICU length of stay were simply continuing to provide care to patients with unsurvivable illness, we would expect their short-term mortality to be quite high—perhaps 75% or more within 90 days of hospital admission. In contrast, if patients remained in the ICU merely because of bed block, we would expect little difference in their mortality compared to shorter-stay patients. Instead, the population-based data, particularly from the US Department of Veterans Affairs, show neither extreme. There is a substantial post-ICU discharge mortality—and higher than among patients with shorter stays—but nothing that would rise to the level of "futile" care or inevitable death.

2.6 Implications of a Persistent Critical Illness Framework

These data suggest that many patients experience persistent critical illness, defined in the sense of experiencing multiple new and cascading problems. In particular, it appears that a major driver at the population level of why patients remain in the ICU is cascading new critical illnesses rather than simple prolonged mechanical ventilation from hypercarbic respiratory failure, failure of presenting complaints to heal, or organizational failures. This has certain implications for both research and the practicing clinician.

In regard to research, a crucial question is whether these cascades are patterned in specific ways. The alternative hypothesis is that such cascades are simply a random aggregation of unlucky events—formally, a Markovian process. If there are specific patterns across organs over time, empirically identifying these regularities might offer deep insights into the structure of multi-organ interdependencies. These would be of prognostic value and might suggest specific subsequences ("motifs") that are highly predictive of adverse events. Such motifs might prove key to a reliable bedside definition of persistent critical illness—and to identifying patients at the cusp of such cascades who would benefit from intensive salvage therapy.

Until such research is done, clinicians must nonetheless care for these patients. A survey suggested that there is a wide range of feasible interventions that clinicians may already be attempting at the bedside [12]. These include aggressive sepsis prevention and control efforts; integrated communication and continuity of care programs, and early mobilization and delirium reduction.

Yet perhaps the most important clinical implication of this work is to remember the dynamism of critically ill patients. As a field, we have come to love the metaphor of the "golden hour." When this metaphor motivates prompt early recognition and life-saving intervention, it is valuable. However, an unintended consequence of the focus on early resuscitation can be to imagine that only the first hours are interesting and dynamic—that the rest of the course of critical illness is only playing out of problems established in that early period. Such a focus exclusively on early resuscitation can lead to inappropriate anchoring and premature diagnostic closure. The persistent critical illness framework reminds us that patients can have new golden hours each day, and constant vigilance is indicated [20, 21].

Take Home Messages

- The differential diagnosis of prolonged ICU stays includes intrinsic patient and admitting diagnostic characteristics, things that happen during the course of critical illness, and organizational failures.
- Existing data suggest that dynamic development of cascading new problems (so called "persistent critical illness") is a major driver at the population level.
- Many patients with prolonged ICU stays do not have persistent respiratory failure; prolonged mechanical ventilation is only a subset of chronic critical illness.

Funding/Support

This work was supported by grants T32 HL007749 from the NIH and IIR 13-079 from the Department of Veterans Affairs Health Services Research & Development service.

Disclosures

This work does not represent the official views of the US Government or Department of Veterans Affairs. The authors have nothing to disclose.

References

1. Kahn JM, Le T, Angus DC, et al. The epidemiology of chronic critical illness in the United States. Crit Care Med. 2015;43:282–7.
2. Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, Morrison RS. The symptom burden of chronic critical illness. Crit Care Med. 2004;32:1527–34.
3. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182:446–54.
4. Mira JC, Gentile LF, Mathias BJ, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45:253–62.
5. Damuth E, Mitchell JA, Bartock JL, Roberts BW, Trzeciak S. Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015;3:544–53.
6. Nelson JE, Tandon N, Mercado AF, Camhi SL, Ely EW, Morrison RS. Brain dysfunction: another burden for the chronically critically ill. Arch Intern Med. 2006;166:1993–9.
7. Iwashyna TJ, Hodgson CL, Pilcher D, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. Lancet Respir Med. 2016;4:566–73.

8. Bagshaw SM, Stelfox HT, Iwashyna TJ, Bellomo R, Zuege D, Wang X. Timing of onset of persistent critical illness: a multi-centre retrospective cohort study. Intensive Care Med. 2018;44(12):2134–44. https://doi.org/10.1007/s00134-018-5440-1.
9. Iwashyna TJ, Hodgson CL, Pilcher D, et al. Towards defining persistent critical illness and other varieties of chronic critical illness. Crit Care Resusc. 2015;17:215–8.
10. Van den Berghe GH. Acute and prolonged critical illness are two distinct neuroendocrine paradigms. Verh K Acad Geneeskd Belg. 1998;60:487–518.
11. Bear DE, Wandrag L, Merriweather JL, et al. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017;21:226.
12. Iwashyna TJ, Hodgson CL, Pilcher D, Bailey M, Bellomo R. Persistent critical illness, as characterized by Australian and New Zealand ICU clinicians. Crit Care Resusc. 2015;17:153–8.
13. Hofer TP, Hayward RA. Are bad outcomes from questionable clinical decisions preventable medical errors? A case of cascade iatrogenesis. Ann Intern Med. 2002;137:327–33.
14. Patera AC, Drewry AM, Chang K, Beiter ER, Osborne D, Hotchkiss RS. Frontline science: defects in immune function in patients with sepsis are associated with PD-1 or PD-L1 expression and can be restored by antibodies targeting PD-1 or PD-L1. J Leukoc Biol. 2016;100:1239–54.
15. Viglianti EM, Kramer R, Admon AJ, et al. Late organ failures in patients with prolonged intensive care unit stays. J Crit Care. 2018;46:55–7.
16. Jeffcote T, Foong M, Gold G, et al. Patient characteristics, ICU-specific supports, complications, and outcomes of persistent critical illness. under review. 2018.
17. Darvall JN, Boonstra T, Norman J, et al. Persistent critical illness: baseline factors, intensive care course, and cause of death. Crit Care Resusc. 2019;21:110–8.
18. Viglianti EM, Kepreos K, Vincent B, et al. Onset of persistent critical illness in a large US integrated healthcare system. Washington, DC: American Thoracic Society; 2017.
19. Viglianti EM, Zajic P, Iwashyna TJ, Amrein K. Neither vitamin D levels nor supplementation are associated with persistent critical illness: a retrospective cohort analysis. Crit Care Resusc. 2019;21:39–44.
20. Kajdacsy-Balla Amaral AC, Barros BS, Barros CC, Innes C, Pinto R, Rubenfeld GD. Nighttime cross-coverage is associated with decreased intensive care unit mortality. A single-center study. Am J Respir Crit Care Med. 2014;189:1395–401.
21. Redelmeier DA. Improving patient care. The cognitive psychology of missed diagnoses. Ann Intern Med. 2005;142:115–20.

Physical Impairment

Contents

Changes in Skeletal Muscle Mass and Contractile Function

J. Batt and C. C. dos Santos

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_3

3

Learning Objectives

Intensive Care Unit Acquired Weakness, a well recognized complication of critical illness, is caused by dysfunction of the neural axis and/or skeletal muscle. It increases ICU and hospital mortality and in the ICU survivor is associated with sustained physical disability, substantially increased health resource utilization and health care costs. To date, there is no intervention that can universally and consistently prevent weakness during critical illness, or enhance its recovery following ICU discharge to improve physical function. The pathophysiology of ICUAW is complex and heterogeneous. This chapter focuses on our current understanding of the pathophysiology driving critical illness myopathy. It reviews the biology behind skeletal muscle loss and dysfunction that occurs in the ICU and can persist in the critical illness survivor. Muscle wasting is a multifactorial process induced by increased muscle proteolysis and decreased protein synthesis in the early phase of critical illness, and the cellular processes and molecular signaling networks responsible will be discussed. Similarly, the biologic processes underpinning impaired muscle contractility are highlighted. The durable impact of critical illness on skeletal muscle biology and the mechanisms resulting in sustained muscle wasting following ICU discharge are also discussed. Current and potential future therapeutic approaches to the prevention and treatment of muscle dysfunction in critical illness and after illness resolution, are proposed.

3.1 Introduction to the Chapter

Intensive care unit-acquired weakness (ICUAW) is a devastating and increasingly common complication of critical illness, exceeding a prevalence of over 70% in certain patient population subgroups [1, 2]. Critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM) comprise ICUAW. Increased patient age, longer duration of ICU stay, sepsis, systemic corticosteroids, female sex, and prolonged sedation are all risk factors for ICUAW development [3–6]. The severity of presentation can vary, with reports of complete quadriplegia in extreme cases [7]. Overall, in the short term ICUAW is associated with increased hospital and 1-year mortality [8]. In the long term, weakness can persist resulting in sustained physical functional disability that compromises quality of life, increases health resource utilization and health care costs, and additionally negatively impacts the survivors' family/caregiver [1, 9–11]. This chapter addresses the skeletal muscle wasting and impairment of contractile function that contributes to ICUAW.

3.2 Impact of Muscle Wasting and Dysfunction in the ICU and Following Discharge

Acute skeletal muscle wasting and impaired contractile function occurs rapidly and early in critical illness, resulting in marked weakness [12, 13]. A multitude of independent risk factors present in the ICU have the capacity to induce muscle wasting and dysfunction including prolonged bedrest and inactivity, systemic and intramuscular inflammation, energy and oxidative stress, neurologic damage, and electrical silencing of the muscle through heavy sedation and neuromuscular blockade [14–16]. Weakness prolongs the duration of mechanical ventilation and ICU stay and is associated with increased ICU mortality. There is marked variability in the recovery potential of skeletal muscle following critical illness resolution—a proportion of survivors will suffer long-term weakness,

while others may expect full to near-complete recovery [1, 9]. The first 3–6 months following ICU discharge are critical, as this is the time frame within which the vast majority of physical functional recovery occurs, before plateauing by 1 year. The physiology underlying the persistent muscle weakness is varied, with some survivors predominantly manifesting sustained muscle wasting, while others regain and normalize muscle mass, but contractility remains diminished [17].

Pre-admission health and functional status, duration of ICU stay, and age all appear to be important risk prognosticators for resilience and long-term functional outcomes following critical illness. We have recently demonstrated that in a population of medical and surgical ICU survivors, discrete disability risk groups are evident, indicated by the functional dependency (total FIM) score calculated at 7 days post ICU discharge [1]. Furthermore, the extent of disability at 7 days post ICU discharge dictates the patients' 1-year mortality and recovery trajectory including ICU and hospital readmission, and subspecialty care use in the first year following ICU discharge. Essentially, critically ill patients younger than 42 years of age who require ICU level care for just or less than 2 weeks will regain normal physical functional status. For example, over 90% of these individuals will be able to bathe and dress independently, and climb stairs 1 year following ICU discharge. In contrast, patients 64 years of age and older, who required ICU care for longer than 2 weeks, were much more likely to demonstrate significant long-term functional dependencies; less than 50% of this cohort were able to bathe, dress, or climb stairs at 1 year after ICU discharge. Poor pre-morbid health status and physical performance have similarly been demonstrated to predict poor physical functional capacity 6 months post ICU discharge [18].

3.3 Muscle Pathology and Mechanisms of Muscle Wasting and Dysfunction

3.3.1 Muscle Pathology

Myopathic changes in CIM include variable degrees of muscle necrosis [19, 20] and myofiber atrophy [17, 21]. The absence of histologic abnormalities has also been reported when the functional defect appears to be solely impaired contractility as opposed to muscle wasting [22]. However, the distinctive feature of the pathology of CIM is the apparent preferential loss of myosin and myosin-related proteins relative to actin [7, 16, 23, 24] as opposed to generalized myofibrillar breakdown. The reasons for this unique pattern of muscle degradation are not well understood. Notably, many standard pre-clinical models of muscle atrophy, including sepsis, muscle unloading/inactivity, and corticosteroid exposure for example, when studied independently, do not reproduce this finding. The development of an "experimental ICU" rodent model of critical illness whereby continuous ventilation is administered in combination with deep anesthesia and other common ICU insults is required to recapitulate the preferential myosin loss [25]. Using such models, it appears that the predominant critical factor for myofibrillar myosinolysis in CIM is the complete mechanical silencing of limb muscle [23, 25–28]. What is unique to the ICU patient, compared to other illness, is the removal of all muscle contractile cues (internal and external) that results from the combination of unloading, inactivity, deep sedation, and/or paralysis to enable mechanical ventilation—which thus appears to be driving a unique muscle pathology [23].

3.3.2 Mechanisms of Muscle Wasting

Given the lack of suitable models of CIM until the development of porcine and rat models of prolonged ventilation not limited by early (1–3 day) mortality, much important work to understand the molecular mechanisms underpinning CIM has also been conducted in ICU patients with and without the phenomenon. Here, associations and correlations with clinical outcomes' measures and changes in the muscle transcriptome, proteome, and enzymatic system function have provided important insights into the molecular regulation of muscle dysfunction in ICUAW.

3.3.2.1 Muscle Proteolysis

Muscle wasting results from an imbalance between proteolysis of structural and contractile proteins and decreased protein synthesis [12, 29–31]. In the early phases of critical illness, proteolytic degradation of muscle is massively upregulated and overwhelms the tissues synthetic capacity. Proteolysis is predominantly regulated be two complementary, but unique, systems—the ubiquitin-proteasome system (UPS) [31] and autophagy [31]. UPS-mediated proteolysis is the process whereby the cell is able to precisely regulate the degradation of proteins by "tagging" them with ubiquitin moieties which act as recognition markers, to activate shuttling of the protein to the 26S proteasome for proteolysis. Ubiquitin ligases are the enzymes that conjugate Ub to the target protein and provide the UPS with specificity by interacting with the target via precise protein–protein interaction domains. In contrast, autophagy is a process whereby an autophagosome is generated that is able to engulf and degrade much larger cellular components including organelles (e.g. mitochondria), cytosol in addition to proteins, but is not as precisely targeted as the UPS.

The UPS is a dominant purveyor of muscle proteolysis in the critically ill [16, 32–34]. Numerous upstream stimuli that are present in the critically ill can induce activation of the muscle UPS system including bedrest and unloading, inflammation, oxidative and energy stress, and alterations in lipid metabolism. Ubiquitin ligases known to be positive regulators of muscle wasting in pre-clinical models of muscle atrophy (denervation, fasting, corticosteroid use), including atrogin-1 and MuRF1 and 2, FBOX31, and SMART, for example, have been shown to be upregulated in experimental models of CIM and the skeletal muscle of patients with CIM, although the relative importance of each remains unclear [16, 25, 26, 35]. The upregulation of MuRF1 and atrogin-1 precedes both the muscle atrophy and the preferential myosin loss that occurs in response to mechanical silencing [25, 27]. Moreover, the temporal upregulation pattern of both is also observed in the diaphragm muscle in the experimental rat ICU model, but this occurs in the absence of the preferential myosin loss, suggesting other proteolytic systems contribute to the myosinolysis [23]. Proteolytic calpains and caspases have been shown to be upregulated in skeletal muscle during critical illness, and may participate in degradation of large actinomyosin complexes for subsequent UPS-mediated proteolysis [16]. In pre-clinical models, protein chaperones, such as heat shock proteins 70 and 90, and αβ-crystallin are quickly upregulated within days of "ICU treatments" [36, 37]. This appears to be a short-term compensatory response to protect against myofibrillar degradation, which will ultimately fail to prevent muscle wasting if the critical illness persists.

While UPS mediated proteolysis occurs extensively and quickly in the early phases of critical illness in the ICU, it is important to note that muscle wasting sustained long-term following ICU discharge does not result from ongoing enhanced UPS activity [17]. Instead, in the critical illness survivor with long-term persistence of muscle wasting, UPS activity

returns to baseline, in keeping with that observed in healthy individuals. Enduring muscle atrophy is the result of an impairment in the muscle's regrowth capacity [17].

Autophagy is a second critical regulator of muscle size, and balanced autophagy is essential to muscle homeostasis, as it enables the removal of damaged cellular components. Thus, the upregulation of autophagy results in muscle proteolysis inducing atrophy, and impaired autophagy, which allows the accumulation of toxic proteins and organelles, also results in muscle wasting [31]. Dysregulation of autophagy has been demonstrated in the atrophic muscle in both humans in the ICU and in animal models [38–42], although there is no evidence of dysregulated autophagy in individuals with sustained muscle wasting months following ICU discharge [17].

The balance between muscle catabolism (protein degradation) and anabolism (protein synthesis) is modulated by delivery of nutrients and exercise [43–45] in health. This homeostatic regulation is lost in the critically ill as neither an increased protein delivery [12, 46, 47] nor early mobility/exercise [48–50] in the ICU has resulted in consistently significant improvement in functional outcomes. These studies show that early aggressive nutrition does neither diminish catabolism nor enhance anabolism. Moreover, early mobility during acute illness may actually delay recovery and aggravate muscle catabolism and dysfunction.

Given the impact of muscle proteolysis on the critical illness outcomes, one might assume inhibition of muscle catabolism would be beneficial. However, one might also speculate that muscle breakdown may serve as an adaptive response, providing a survival benefit by deprioritizing an energy-dependent non-vital organ, liberating amino acids for consumption during critical illness. There is data to support both premises [51–53]. Thus, any attempt to inhibit proteolysis to spare muscle may need to be carefully considered with respect to both timing and extent. Bortezomib, a pharmacologic inhibitor of the proteasome approved for clinical use in specific malignancies, decreases the extent of muscle wasting in some (e.g. denervation) but not all (e.g. cancer) pre-clinical models of muscle atrophy [54–57]. Bortezomib has been shown to partially inhibit diaphragm weakness in mechanically ventilated animals [58], but its effects on limb skeletal muscle mass and power in pre-clinical models of CIM and the critically ill patient remain to be evaluated.

3.3.2.2 Muscle Protein Synthesis and Regeneration

Skeletal muscle protein synthesis and anabolism is upregulated by multiple stimuli including static muscle stretch, muscle loading, autocrine and endocrine growth factors, and positive energy balance. These various stimuli signal downstream within myocytes via both the canonical IGF/AKT/mTOR signaling network, and in an AKT-independent, mTOR-dependent manner, contingent upon the specific stimulus applied [23, 59]. mTOR1 is a key and essential regulator of protein synthesis, positively regulating mRNA translation and leading to muscle hypertrophy [59]. In the critically ill, muscle protein synthesis has been reported to be variably increased or impaired, depending upon the patient population assessed, timing of the study assessment, and therapies applied [12, 60–64]. Protein turnover is increased in critical illness in the early days of ICU admission, possibly as a compensatory response to massive proteolytic stimuli.

Over the past decade, studies in cell culture and pre-clinical models evaluating the molecular regulation of protein homeostasis in muscle have clearly demonstrated that proteolytic and anabolic signaling networks are reciprocally linked. Downregulation of AKT/mTOR signaling not only disables mRNA translation and protein synthesis, but

concomitantly enables upregulation of autophagy and UPS-mediated proteolysis [30] and vice versa. Most recently, Puthucheary and colleagues demonstrated that intramuscular inflammatory and hypoxia cellular signaling combined with reduced ATP bioavailability, all factors well known to activate proteolytic systems, was directly and robustly correlated with impaired muscle anabolic signaling and the development of atrophy within the early days of critical illness and ICU admission [64]. This is in keeping with previous work demonstrating widespread dephosphorylation of proteins in anabolic signaling networks (Akt1, GSK3α β, mTOR, p70S6K, and 4E-BP1) in the muscle of critically ill patients in the ICU, despite concurrent increases in their mRNA levels [35].

In contrast to the massively upregulated proteolysis and anabolic resistance reported early in critical illness in the ICU, in the long-term survivor, the molecular regulation of sustained muscle wasting has not been well studied. Our group was the first to demonstrate that the skeletal muscle UPS and autophagy networks were normalized in the critical illness survivor 6 months following ICU discharge. Instead of continued enhanced proteolytic-mediated loss of muscle, the recovery of muscle mass appeared to be impaired [17]. We found a reduced number of myogenic stem (satellite) cells in the persistently atrophic muscle of patients, suggesting that impaired muscle regeneration may contribute to the long-term muscle wasting of sustained ICUAW, although we did not specifically test this premise. Moreover, we did not determine whether the diminished satellite cell population demonstrated any functional limitations. In a pre-clinical model of sepsis, the depletion of satellite cells occurred as a result of increased apoptosis and an impairment in their self-renewal capacity [65]. This culminated in diminished muscle regeneration and persistent weakness 3 months following sepsis resolution, showing that the satellite cell population was durably altered by a single episode of sepsis.

3.3.2.3 Skeletal Muscle Mitochondria Content and Function

Mitochondria are essential to maintain muscle energy status and contractile function. In both pre-clinical models of CIM and critically ill patients in the ICU, muscle mitochondria are reported to be decreased in number, and EM studies have revealed mitochondrial ultrastructural damage [64, 66–70]. Compromised mitochondrial function in muscle will (i) impair muscle mechano-sensing, (ii) increase production of reactive oxygen species, (iii) induce cytopathic hypoxia, and (iv) result in muscle ATP depletion [71, 72], all of which are capable of stimulating proteolytic signaling networks and down regulating protein synthesis networks, thus culminating in muscle wasting. We reported that the differential expression of mitochondrial-related genes in a transcriptomic analysis of muscle biopsies obtained from patients with and without sustained muscle wasting 6 months after ICU discharge was robustly correlated with resolution of muscle atrophy and recovery of strength [73]. Functional enrichment revealed these genes regulated mitochondrial biogenesis and ATP synthesis.

Pre-clinical studies have also demonstrated the regulation of mitochondrial size and shape may directly impact muscle size independently of the mechanisms described above. Mitochondria continuously change in shape, number, and cellular localization within muscle due to continuous alteration between fission and fusion events. Fusion creates a network of connected mitochondria that enables exchange of their content to maintain the integrity of the mitochondrial genome and proteome [74, 75]. In contrast, fission creates smaller mitochondria that can function individually within the cell or be degraded by mitophagy [76]. There is evidence to suggest that regulation of mitochondrial size

via fusion and fission in itself may play a critical role in the muscle wasting of CIM. In pre-clinical models of muscle mass regulation, genetic deletion of Mfn1 and Mfn2, both mitochondrial fusion proteins, induces muscle wasting [77, 78]. Conversely, overexpression of Drp1 and Fis1, two proteins that induce mitochondrial fission, results in increased autophagy and muscle atrophy in rodents [77, 78]. While the regulation of mitochondrial fission and fusion in the muscle of critically ill patient has yet to be evaluated, one might speculate alterations in the homeostatic balance maintained in health may contribute to the loss of muscle seen acutely in the critically ill patient.

Whether mitochondrial abnormalities contribute to the persistent muscle atrophy seen longer term in survivors with sustained ICUAW is unknown. We reported that muscle mitochondrial number, density, and size in patients with and without sustained muscle atrophy 6 months following ICU discharge had returned to baseline levels seen in healthy "normal" individuals [17]. However, we did not evaluate mitochondrial fission or fusion, nor did we evaluate the expression of the proteins known to regulate either process in these survivors.

3.3.2.4 microRNA Regulation of Muscle

MicroRNAs (miRs) are small non-coding RNAs that regulate gene expression by modulating the degradation or translation of large sets of mRNAs. As such, they are able to rapidly and broadly impact cellular functions by impacting key regulatory elements in whole signaling networks simultaneously. Within muscle, miRs can act locally in an autocrine manner, or in a paracrine fashion circulating within the bloodstream, to impact myogenesis and muscle size [79, 80]. A handful of miRs identified as "myomiRs" (miR-1, miR-133, miR-206, and miR-208)—their expression is restricted to skeletal muscle—are well known to regulate critical cellular signaling networks that control protein synthesis and fibrosis within muscle, and myogenic differentiation, including the AKT/PI3K/mTOR and TGFβ networks [79, 81]. To date, very few studies have evaluated miR regulation of CIM, but given the rapidity of critical illness-induced changes in muscle, and muscle's plasticity, the likely highly influential impact of miRs in the pathology of CIM, and muscles recovery, makes good biologic sense.

Recently, miR-542-3p/5p has been shown to induce muscle atrophy in ICU patients via promotion of mitochondrial dysfunction and enhanced TGFβ signaling [82]. Paul and colleagues identified quadriceps expression of miR-422a to be positively associated with strength and retention of mass in individuals admitted to the ICU following elective aortic surgery, despite very short admissions across all patients (all less than 7 days) [83]. In a paired miR-mRNA co-expression analysis of quadriceps muscle biopsies from patients with and without sustained ICUAW, we found 20 miRs significantly regulated the differential gene signature at day 7 post ICU discharge, with miR-424-5p regulating 23% of all DE genes, suggesting its role as a master regulator of early ICUAW (unpublished data). Furthermore, at month 6 post ICU discharge, distinct miR expression signatures were found to separate ICUAW patients with significant improvement in muscle mass from those with little gain (unpublished data).

miRs are of significant importance in the future management of ICUAW, since they can both serve as therapeutic agents, concurrently targeting multiple cellular signaling networks, and thus have a broad impact on muscle biology, in addition to functioning as biomarkers of disease or response to therapy, given they are secreted into the bloodstream [80, 84].

3.3.2.5 Metabolic Reprogramming of Muscle

Lipid toxicity has been reported to contribute to diaphragmatic dysfunction with mechanical ventilation [85]. Accelerated lipolysis, as occurs in the catabolic phase of critical illness, results in the systemic release of triglyceride-rich lipoproteins and free fatty acids (FFA) into the bloodstream that may be ultimately toxic to muscle cells [86–89]. In animal models, ectopic lipid accumulation induces proteasomal activity, apoptosis, and skeletal muscle damage. Interestingly, overexpression of lipoprotein lipase, the key enzyme in lipolysis, induced loss of myogenic potential in murine C2C12 myoblasts [89]. Whether lipid toxicity may contribute to the depletion of satellite cells in the critically ill patient remains to be evaluated. Moreover, in contrast to the aforementioned studies, neither muscle mass nor muscle ATP content was impacted by the quantity of fatty acids delivered as nutritional supplements to critically ill patients within the first 7 days of ICU admission [64].

3.3.2.6 Peripheral Nerve Injury

While CIM occurs in the absence of CIP in many patients with ICUAW, it is important to keep in mind that any injury to the peripheral nervous system will provide additional stimulus for the rapid recruitment of the muscle proteolytic machinery and downregulation of muscle anabolic signaling. Prolonged traumatic muscle denervation will cause severe muscle atrophy and subsequent fibrosis [90]. Prolonged CIP resulting in long-term functional denervation could theoretically have the same impact on muscle biology in the critically ill. Long-term neuromuscular junction (NMJ) dysfunction and degradation contributes to muscle atrophy, as occurs in age-dependent sarcopenia [91, 92]. However, whether short-term neuromuscular blockade plays a role in CIM remains controversial [93, 94].

3.3.3 Mechanisms of Muscle Contractile Failure

3.3.3.1 Dissociation Between Muscle Form and Function

In aging, a discordance between muscle size and strength occurs; weakness exceeds that expected for the loss of muscle mass due to degenerative changes within the neuroaxis and muscle [95]. A dissociation of mass and contractile capacity can also be evident in ICUAW. In the pre-clinical CIM model (sustained mechanical ventilation with paralysis and sedation), the preferential myosin loss relative to actin changes the character of muscle, such that its contractility is impaired. Where loss of muscle ranges between 25% and 50% within 14 days of institution of mechanical ventilation, a 65% decrease in muscle-specific force occurs [25, 37]. Likewise, we found marked heterogeneity in muscle outcomes 6 months following ICU discharge. A proportion of critical illness survivors demonstrated predominantly impaired contractility in the face of normalization of their muscle mass 6 months following ICU discharge, again highlighting the potential disconnect between muscle mass and strength [17].

The force-generating capacity of muscle in the ICU is decreased by alteration in muscle composition (e.g. necrosis, fatty infiltration) and critical illness neuropathy (if present). Altered cellular signaling and Ca++ handling within the muscle also impede contractile function directly. Pre-clinical models of CIM demonstrate that the cause of decrements in muscle-specific force (force generated/unit of muscle mass) is multifactorial, resulting from altered bioenergetics with depletion of ATP due to mitochondrial loss and dysfunction (as previously discussed), altered muscle membrane excitability, and muscle excitation–contraction uncoupling [16, 96].

Diminished muscle membrane excitability has been repeatedly reported in critically ill patients and is manifested as decreased conduction velocity, increased relative refractory periods, and reduced fiber excitability in response to direct muscle stimulation [97–101]. The steroid-denervation model of CIM, which consists of tibial or sciatic nerve transection with denervation of the hindlimb musculature accompanied by the systemic administration of corticosteroids, has served as the primary pre-clinical model with which to study the mechanisms underpinning the diminished muscle excitability. Keeping in mind the limitations of employing this pre-clinical CIM model to study mechanisms, a "sodium channelopathy" appears to be acquired which alters both the muscle baseline resting membrane potential and depolarization in response to an action potential [102, 103]. This channelopathy consists of a change in the proportion of channel isoform expression and a hyperpolarized shift in the voltage dependence of the channel inactivation, although it is felt that it is primarily the shift in the voltage dependency of the $Na\ 1.4_v$ isoform that results in the membrane hypoexcitability [104, 105]. The pro-inflammatory milieu encountered in critical illness (e.g. TNFα, CNTF) [106–108] plays a contributory role in the induction of the sodium channelopathy. Abnormalities of other membrane channels, including function of the ryanodine and L-type Ca^{+2} channels, have also been reported to influence muscle membrane excitability in critical illness models [109, 110].

Muscle contraction is generated by the release of Ca^{+2} from the sarcoplasmic reticulum to the cytosol where it stimulates the interaction between myosin and troponin. In health, the electrical signal transmitted by the peripheral nerve motor neuron depolarizes the muscle membrane, stimulating the release of Ca^{+2} to induce a contraction, and is referred to as excitation–contraction coupling. Excitation–contraction uncoupling induced by altered intracellular calcium homeostasis has been demonstrated extensively in sepsis and systemic inflammation [16, 111, 112]. Abnormalities in calcium handling, due to altered membrane receptors/ion channels (i.e. ryanodine receptor) and reduced sensitivity of myofilaments to Ca^{+2} due to posttranslation modifications of the myofilaments, contribute to the excitation–contraction uncoupling reported in the rodent experimental ICU model [25, 113, 114]. Of note, administration of the chaperone co-inducer BGP-15 in a pre-clinical model of ventilator-induced diaphragmatic dysfunction restored the muscle-specific force to approximately 75% of its original value [115] by protecting myosin from detrimental posttranslational modifications.

3.4 Therapeutic Approaches to the Prevention and Treatment of CIM

We currently have no consistently effective therapy to prevent or treat CIM. For well over a decade now, proponents of early mobility/exercise and neuromuscular stimulation (NMES) in the ICU have promoted their use in the critically ill, with some success [2]. If applied early enough in the course of illness, and administered with the combined effort to minimize sedation protocols and paralysis, short-term physical functional outcomes can be improved. However, well-designed randomized trials to evaluate the impact in the long term (months following ICU discharge) remain to be completed.

Pharmacologic interventions for muscle wasting and weakness in the ICU must contend with the biphasic nature of CIM. Treatment in the initial stages will need to focus on counteracting the enhanced catabolism, while keeping in mind the potential survival advantage conferred by "deprioritizing" an energy expensive non-vital organ. As noted previously, the

timing and extent of inhibition will need to be carefully considered. Alternative approaches in the ICU would be to combat the anabolic resistance. Much work is being undertaken to optimize the timing and type of feeding in the critically ill patient to mitigate, or at least not exacerbate proteolysis and counteract the anabolic resistance in the acute phases, and to optimize outcomes in later reparative phases of CIM. Given the potential for lipid-induced muscle toxicity and the fact that lipid delivery has little effect on muscle energy stores [64], the use of non-fat food sources and removal of fatty acid supplementation should be considered and trialed. In addition, given the association of intramuscular inflammation with impairment of anabolic signaling and muscle wasting in the early acute phase of critical illness, evaluations of anti-inflammatory agents at this time should be considered [64]. Treatments for impaired contractility can begin to focus on modulation of the sodium and calcium channels, and the development of chaperones to protect myofibrillar proteins from detrimental posttranslational modifications. Finally, the potential impact miRs and their antagonists may have on muscle in critical illness is an area of great potential for investigation, given the ability to serve as therapeutic agents as well as biomarkers [80, 84]. However, regardless of the preventative or treatment modality trialed, it will be extremely important to keep in mind that the heterogeneity in case mix and the uncertainty that randomization can account for different ICU lengths of stay and injury accrued over time, as the ICU stay extends, may make it complicated and difficult to show benefit.

Conclusion

Early and sustained ICUAW is a prevalent and significant problem with no effective therapies. The pathophysiology is complex and heterogeneous, affecting multiple organ systems and biological processes. Recently, landmark clinical studies have demonstrated that clinical parameters, such as age and duration of ICU level care, can partially resolve patient heterogeneity and enable prognostic enrichment (identifying those patients at greatest risk of adverse outcome). Prognostic enrichment in future trials may allow us to design and administer particular interventions in subpopulations of patients that are more likely to be at risk for acute and sustained ICUAW. Importantly, as we develop novel therapeutic alternatives on the bench, translating that knowledge to the bedside will require that we develop the tools to identify those patients most likely to benefit from a particular therapy. Tools for therapeutic enrichment are markedly lacking, and our assessment measures fail to characterize and quantify dysregulated biological responses and therefore are unable to appropriately align patients with emerging therapies to achieve the personalization necessary to improve care. As we move forward, further studies aimed at understanding, characterizing, and quantifying the pathophysiology of ICUAW and of sustained muscle dysfunction will be fundamental to impart significant impact on care.

References

1. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med. 2016;194(7):831–44.
2. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med. 2017;43(9):1270–81.
3. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American thoracic society clinical practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014;190(12):1437–46.

4. Yang T, Li Z, Jiang L, Wang Y, Xi X. Risk factors for intensive care unit-acquired weakness: a systematic review and meta-analysis. Acta Neurol Scand. 2018;138(2):104–14.
5. Yang T, Li Z, Jiang L, Xi X. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. Crit Care. 2018;22(1):187.
6. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, et al. Risk factors for physical impairment after acute lung injury in a national, multicenter study. Am J Respir Crit Care Med. 2014;189(10):1214–24.
7. Larsson L, Li X, Edstrom L, Eriksson LI, Zackrisson H, Argentini C, et al. Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: mechanisms at the cellular and molecular levels. Crit Care Med. 2000;28(1):34–45.
8. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20.
9. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
10. Cameron JI, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. One-year outcomes in caregivers of critically ill patients. N Engl J Med. 2016;374(19):1831–41.
11. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med. 2010;153(3):167–75.
12. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
13. Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med. 2013;187(3):238–46.
14. Trappe S, Trappe T, Gallagher P, Harber M, Alkner B, Tesch P. Human single muscle fibre function with 84 day bed-rest and resistance exercise. J Physiol. 2004;557(Pt 2):501–13.
15. Irimia JM, Guerrero M, Rodriguez-Miguelez P, Cadefau JA, Tesch PA, Cusso R, et al. Metabolic adaptations in skeletal muscle after 84 days of bed rest with and without concurrent flywheel resistance exercise. J Appl Physiol (1985). 2017;122(1):96–103.
16. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev. 2015;95(3):1025–109.
17. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.
18. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors associated with functional recovery among older intensive care unit survivors. Am J Respir Crit Care Med. 2016;194(3):299–307.
19. Hund E. Myopathy in critically ill patients. Crit Care Med. 1999;27(11):2544–7.
20. Helliwell TR, Coakley JH, Wagenmakers AJ, Griffiths RD, Campbell IT, Green CJ, et al. Necrotizing myopathy in critically-ill patients. J Pathol. 1991;164(4):307–14.
21. Lacomis D, Giuliani MJ, Van Cott A, Kramer DJ. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. Ann Neurol. 1996;40(4):645–54.
22. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10(10):931–41.
23. Kalamgi RC, Larsson L. Mechanical signaling in the pathophysiology of critical illness myopathy. Front Physiol. 2016;7:23.
24. Llano-Diez M, Renaud G, Andersson M, Marrero HG, Cacciani N, Engquist H, et al. Mechanisms underlying ICU muscle wasting and effects of passive mechanical loading. Crit Care. 2012;16(5):R209.
25. Ochala J, Gustafson AM, Diez ML, Renaud G, Li M, Aare S, et al. Preferential skeletal muscle myosin loss in response to mechanical silencing in a novel rat intensive care unit model: underlying mechanisms. J Physiol. 2011;589(Pt 8):2007–26.
26. Corpeno Kalamgi R, Salah H, Gastaldello S, Martinez-Redondo V, Ruas JL, Fury W, et al. Mechanosignalling pathways in an experimental intensive critical illness myopathy model. J Physiol. 2016;594(15):4371–88.
27. Renaud G, Llano-Diez M, Ravara B, Gorza L, Feng HZ, Jin JP, et al. Sparing of muscle mass and function by passive loading in an experimental intensive care unit model. J Physiol. 2013;591(5):1385–402.

28. Rossignol B, Gueret G, Pennec JP, Morel J, Rannou F, Giroux-Metges MA, et al. Effects of chronic sepsis on contractile properties of fast twitch muscle in an experimental model of critical illness neuromyopathy in the rat. Crit Care Med. 2008;36(6):1855–63.
29. Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, et al. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. 2014;40(4):528–38.
30. Schiaffino S, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. FEBS J. 2013;280(17):4294–314.
31. Sandri M. Protein breakdown in muscle wasting: role of autophagy-lysosome and ubiquitin-proteasome. Int J Biochem Cell Biol. 2013;45(10):2121–9.
32. Derde S, Hermans G, Derese I, Guiza F, Hedstrom Y, Wouters PJ, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med. 2012;40(1):79–89.
33. Klaude M, Fredriksson K, Tjader I, Hammarqvist F, Ahlman B, Rooyackers O, et al. Proteasome proteolytic activity in skeletal muscle is increased in patients with sepsis. Clin Sci (Lond). 2007;112(9):499–506.
34. Klaude M, Mori M, Tjader I, Gustafsson T, Wernerman J, Rooyackers O. Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci (Lond). 2012;122(3):133–42.
35. Constantin D, McCullough J, Mahajan RP, Greenhaff PL. Novel events in the molecular regulation of muscle mass in critically ill patients. J Physiol. 2011;589(Pt 15):3883–95.
36. Banduseela VC, Ochala J, Chen YW, Goransson H, Norman H, Radell P, et al. Gene expression and muscle fiber function in a porcine ICU model. Physiol Genomics. 2009;39(3):141–59.
37. Friedrich O, Diermeier S, Larsson L. Weak by the machines: muscle motor protein dysfunction – a side effect of intensive care unit treatment. Acta Physiol (Oxf). 2018;222(1):1–14.
38. Hussain SN, Mofarrahi M, Sigala I, Kim HC, Vassilakopoulos T, Maltais F, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. Am J Respir Crit Care Med. 2010;182(11):1377–86.
39. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Guiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011;96(4):E633–45.
40. Mofarrahi M, Sigala I, Guo Y, Godin R, Davis EC, Petrof B, et al. Autophagy and skeletal muscles in sepsis. PLoS One. 2012;7(10):e47265.
41. Llano-Diez M, Gustafson AM, Olsson C, Goransson H, Larsson L. Muscle wasting and the temporal gene expression pattern in a novel rat intensive care unit model. BMC Genomics. 2011;12:602.
42. Banduseela VC, Chen YW, Kultima HG, Norman HS, Aare S, Radell P, et al. Impaired autophagy, chaperone expression, and protein synthesis in response to critical illness interventions in porcine skeletal muscle. Physiol Genomics. 2013;45(12):477–86.
43. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care. 2015;19(Suppl 3):S6.
44. Heyland DK, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, et al. Combining nutrition and exercise to optimize survival and recovery from critical illness: conceptual and methodological issues. Clin Nutr. 2016;35(5):1196–206.
45. Bear DE, Puthucheary ZA, Hart N. Early feeding during critical illness. Lancet Respir Med. 2014;2(1):15–7.
46. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385–93.
47. Casaer MP, Wilmer A, Van den Berghe G. Supplemental parenteral nutrition in critically ill patients. Lancet. 2013;381(9879):1715.
48. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. JAMA. 2016;315(24):2694–702.
49. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10.
50. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med. 2016;193(10):1101–10.
51. Fischer D, Gang G, Pritts T, Hasselgren PO. Sepsis-induced muscle proteolysis is prevented by a proteasome inhibitor in vivo. Biochem Biophys Res Commun. 2000;270(1):215–21.

52. Bach HH, Laporte HM, Wong YM, Gamelli RL, Majetschak M. Proteasome inhibition prolongs survival during lethal hemorrhagic shock in rats. J Trauma Acute Care Surg. 2013;74(2):499–507.
53. Vana PG, LaPorte HM, Wong YM, Kennedy RH, Gamelli RL, Majetschak M. Proteasome inhibition after burn injury. J Burn Care Res. 2016;37(4):207–15.
54. Lang CH, Huber D, Frost RA. Burn-induced increase in atrogin-1 and MuRF-1 in skeletal muscle is glucocorticoid independent but downregulated by IGF-I. Am J Physiol Regul Integr Comp Physiol. 2007;292(1):R328–36.
55. Beehler BC, Sleph PG, Benmassaoud L, Grover GJ. Reduction of skeletal muscle atrophy by a proteasome inhibitor in a rat model of denervation. Exp Biol Med (Maywood). 2006;231(3):335–41.
56. Gazzerro E, Assereto S, Bonetto A, Sotgia F, Scarfi S, Pistorio A, et al. Therapeutic potential of proteasome inhibition in Duchenne and Becker muscular dystrophies. Am J Pathol. 2010;176(4):1863–77.
57. Penna F, Bonetto A, Aversa Z, Minero VG, Rossi Fanelli F, Costelli P, et al. Effect of the specific proteasome inhibitor bortezomib on cancer-related muscle wasting. J Cachexia Sarcopenia Muscle. 2016;7(3):345–54.
58. Agten A, Maes K, Thomas D, Cielen N, Van Hees HW, Dekhuijzen RP, et al. Bortezomib partially protects the rat diaphragm from ventilator-induced diaphragm dysfunction. Crit Care Med. 2012;40(8):2449–55.
59. Yoon MS. mTOR as a key regulator in maintaining skeletal muscle mass. Front Physiol. 2017;8:788.
60. Jespersen JG, Nedergaard A, Reitelseder S, Mikkelsen UR, Dideriksen KJ, Agergaard J, et al. Activated protein synthesis and suppressed protein breakdown signaling in skeletal muscle of critically ill patients. PLoS One. 2011;6(3):e18090.
61. Biolo G, Fleming RY, Maggi SP, Nguyen TT, Herndon DN, Wolfe RR. Inverse regulation of protein turnover and amino acid transport in skeletal muscle of hypercatabolic patients. J Clin Endocrinol Metab. 2002;87(7):3378–84.
62. Glover EI, Phillips SM, Oates BR, Tang JE, Tarnopolsky MA, Selby A, et al. Immobilization induces anabolic resistance in human myofibrillar protein synthesis with low and high dose amino acid infusion. J Physiol. 2008;586(24):6049–61.
63. Drummond MJ, Dickinson JM, Fry CS, Walker DK, Gundermann DM, Reidy PT, et al. Bed rest impairs skeletal muscle amino acid transporter expression, mTORC1 signaling, and protein synthesis in response to essential amino acids in older adults. Am J Physiol Endocrinol Metab. 2012;302(9):E1113–22.
64. Puthucheary ZA, Astin R, McPhail MJW, Saeed S, Pasha Y, Bear DE, et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax. 2018;73(10):926–35.
65. Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun. 2015;6:10145.
66. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–23.
67. Fredriksson K, Hammarqvist F, Strigard K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab. 2006;291(5):E1044–50.
68. Crouser ED, Julian MW, Blaho DV, Pfeiffer DR. Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. Crit Care Med. 2002;30(2):276–84.
69. Rooyackers OE, Gijsen AP, Saris WH, Soeters PB, Wagenmakers AJ. Derangement in aerobic and anaerobic energy metabolism in skeletal muscle of critically ill and recovering rats. Biochim Biophys Acta. 1996;1315(1):55–60.
70. Carre JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010;182(6):745–51.
71. Wang N, Naruse K, Stamenovic D, Fredberg JJ, Mijailovich SM, Tolic-Norrelykke IM, et al. Mechanical behavior in living cells consistent with the tensegrity model. Proc Natl Acad Sci U S A. 2001;98(14):7765–70.
72. Romanello V, Sandri M. Mitochondrial quality control and muscle mass maintenance. Front Physiol. 2015;6:422.
73. Walsh CJ, Batt J, Herridge MS, Mathur S, Bader GD, Hu P, et al. Transcriptomic analysis reveals abnormal muscle repair and remodeling in survivors of critical illness with sustained weakness. Sci Rep. 2016;6:29334.
74. Chen H, Chan DC. Emerging functions of mammalian mitochondrial fusion and fission. Hum Mol Genet. 2005;14 Spec No. 2:R283–9.

75. Tondera D, Grandemange S, Jourdain A, Karbowski M, Mattenberger Y, Herzig S, et al. SLP-2 is required for stress-induced mitochondrial hyperfusion. EMBO J. 2009;28(11):1589–600.
76. Elgass K, Pakay J, Ryan MT, Palmer CS. Recent advances into the understanding of mitochondrial fission. Biochim Biophys Acta. 2013;1833(1):150–61.
77. Romanello V, Guadagnin E, Gomes L, Roder I, Sandri C, Petersen Y, et al. Mitochondrial fission and remodelling contributes to muscle atrophy. EMBO J. 2010;29(10):1774–85.
78. Chen H, Vermulst M, Wang YE, Chomyn A, Prolla TA, McCaffery JM, et al. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. Cell. 2010;141(2):280–9.
79. Wang XH. MicroRNA in myogenesis and muscle atrophy. Curr Opin Clin Nutr Metab Care. 2013;16(3):258–66.
80. De Guire V, Robitaille R, Tetreault N, Guerin R, Menard C, Bambace N, et al. Circulating miRNAs as sensitive and specific biomarkers for the diagnosis and monitoring of human diseases: promises and challenges. Clin Biochem. 2013;46(10–11):846–60.
81. Nakasa T, Ishikawa M, Shi M, Shibuya H, Adachi N, Ochi M. Acceleration of muscle regeneration by local injection of muscle-specific microRNAs in rat skeletal muscle injury model. J Cell Mol Med. 2010;14(10):2495–505.
82. Garros RF, Paul R, Connolly M, Lewis A, Garfield BE, Natanek SA, et al. MicroRNA-542 promotes mitochondrial dysfunction and SMAD activity and is elevated in intensive care unit-acquired weakness. Am J Respir Crit Care Med. 2017;196(11):1422–33.
83. Paul R, Lee J, Donaldson AV, Connolly M, Sharif M, Natanek SA, et al. miR-422a suppresses SMAD4 protein expression and promotes resistance to muscle loss. J Cachexia Sarcopenia Muscle. 2018;9(1):119–28.
84. Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee SS. Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine. Mol Ther Nucleic Acids. 2017;8:132–43.
85. Mrozek S, Jung B, Petrof BJ, Pauly M, Roberge S, Lacampagne A, et al. Rapid onset of specific diaphragm weakness in a healthy murine model of ventilator-induced diaphragmatic dysfunction. Anesthesiology. 2012;117(3):560–7.
86. Ilias I, Vassiliadi DA, Theodorakopoulou M, Boutati E, Maratou E, Mitrou P, et al. Adipose tissue lipolysis and circulating lipids in acute and subacute critical illness: effects of shock and treatment. J Crit Care. 2014;29(6):1130 e5–9.
87. Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. Crit Care Med. 2013;41(1):317–25.
88. Hauck AK, Bernlohr DA. Oxidative stress and lipotoxicity. J Lipid Res. 2016;57(11):1976–86.
89. Tamilarasan KP, Temmel H, Das SK, Al Zoughbi W, Schauer S, Vesely PW, et al. Skeletal muscle damage and impaired regeneration due to LPL-mediated lipotoxicity. Cell Death Dis. 2012;3:e354.
90. Carlson BM. The biology of long-term denervated skeletal muscle. Eur J Transl Myol. 2014;24(1):3293.
91. Tudorascu I, Sfredel V, Riza AL, Danciulescu Miulescu R, Ianosi SL, Danoiu S. Motor unit changes in normal aging: a brief review. Romanian J Morphol Embryol. 2014;55(4):1295–301.
92. Curcio F, Ferro G, Basile C, Liguori I, Parrella P, Pirozzi F, et al. Biomarkers in sarcopenia: a multifactorial approach. Exp Gerontol. 2016;85:1–8.
93. Puthucheary Z, Rawal J, Ratnayake G, Harridge S, Montgomery H, Hart N. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? Am J Respir Crit Care Med. 2012;185(9):911–7.
94. Wilcox SR. Corticosteroids and neuromuscular blockers in development of critical illness neuromuscular abnormalities: a historical review. J Crit Care. 2017;37:149–55.
95. Manini TM, Clark BC. Dynapenia and aging: an update. J Gerontol A Biol Sci Med Sci. 2012;67(1):28–40.
96. Batt J, Mathur S, Katzberg HD. Mechanism of ICU-acquired weakness: muscle contractility in critical illness. Intensive Care Med. 2017;43(4):584–6.
97. Weber-Carstens S, Koch S, Spuler S, Spies CD, Bubser F, Wernecke KD, et al. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients. Crit Care Med. 2009;37(9):2632–7.
98. Trojaborg W. Electrophysiologic techniques in critical illness-associated weakness. J Neurol Sci. 2006;242(1–2):83–5.
99. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology. 1996;46(3):731–6.

100. Lefaucheur JP, Nordine T, Rodriguez P, Brochard L. Origin of ICU acquired paresis determined by direct muscle stimulation. J Neurol Neurosurg Psychiatry. 2006;77(4):500–6.
101. Z'Graggen WJ, Brander L, Tuchscherer D, Scheidegger O, Takala J, Bostock H. Muscle membrane dysfunction in critical illness myopathy assessed by velocity recovery cycles. Clin Neurophysiol. 2011;122(4):834–41.
102. Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. J Physiol. 2003;547(Pt 2):555–66.
103. Rich MM, Pinter MJ. Sodium channel inactivation in an animal model of acute quadriplegic myopathy. Ann Neurol. 2001;50(1):26–33.
104. Kraner SD, Novak KR, Wang Q, Peng J, Rich MM. Altered sodium channel-protein associations in critical illness myopathy. Skelet Muscle. 2012;2(1):17.
105. Filatov GN, Rich MM. Hyperpolarized shifts in the voltage dependence of fast inactivation of Nav1.4 and Nav1.5 in a rat model of critical illness myopathy. J Physiol. 2004;559(Pt 3):813–20.
106. Guillouet M, Rannou F, Giroux-Metges MA, Droguet M, Pennec JP. Tumor necrosis factor alpha induced hypoexcitability in rat muscle evidenced in a model of ion currents and action potential. Cytokine. 2013;64(1):165–71.
107. Guillouet M, Gueret G, Rannou F, Giroux-Metges MA, Gioux M, Arvieux CC, et al. TNFalpha increases resting potential in isolated fibres from rat peroneus longus by a PKC mediated mechanism: involvement in ICU acquired polyneuromyopathy. Cytokine. 2011;56(2):149–52.
108. Guillard E, Gueret G, Guillouet M, Vermeersch V, Rannou F, Giroux-Metges MA, et al. Alteration of muscle membrane excitability in sepsis: possible involvement of ciliary nervous trophic factor (CNTF). Cytokine. 2013;63(1):52–7.
109. Kraner SD, Wang Q, Novak KR, Cheng D, Cool DR, Peng J, et al. Upregulation of the CaV 1.1-ryanodine receptor complex in a rat model of critical illness myopathy. Am J Physiol Regul Integr Comp Physiol. 2011;300(6):R1384–91.
110. Friedrich O, Hund E, von Wegner F. Enhanced muscle shortening and impaired Ca2+ channel function in an acute septic myopathy model. J Neurol. 2010;257(4):546–55.
111. Callahan LA, Nethery D, Stofan D, DiMarco A, Supinski G. Free radical-induced contractile protein dysfunction in endotoxin-induced sepsis. Am J Respir Cell Mol Biol. 2001;24(2):210–7.
112. Hardin BJ, Campbell KS, Smith JD, Arbogast S, Smith J, Moylan JS, et al. TNF-alpha acts via TNFR1 and muscle-derived oxidants to depress myofibrillar force in murine skeletal muscle. J Appl Physiol (1985). 2008;104(3):694–9.
113. Friedrich O, Yi B, Edwards JN, Reischl B, Wirth-Hucking A, Buttgereit A, et al. IL-1alpha reversibly inhibits skeletal muscle ryanodine receptor. A novel mechanism for critical illness myopathy? Am J Respir Cell Mol Biol. 2014;50(6):1096–106.
114. Llano-Diez M, Cheng AJ, Jonsson W, Ivarsson N, Westerblad H, Sun V, et al. Impaired Ca(2+) release contributes to muscle weakness in a rat model of critical illness myopathy. Crit Care. 2016;20(1):254.
115. Salah H, Li M, Cacciani N, Gastaldello S, Ogilvie H, Akkad H, et al. The chaperone co-inducer BGP-15 alleviates ventilation-induced diaphragm dysfunction. Sci Transl Med. 2016;8(350):350ra103.

Critical Illness Neuromyopathy: Clinical, Electrophysiological, and Histological Diagnosis

Nicola Latronico and Greet Hermans

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_4

Learning Objectives

- To appreciate the incidence and context of neuromuscular complications in critically ill patients and to understand the underlying neuromuscular alterations.
- To be able to describe the clinical features of critical illness neuromyopathy.
- To be able to describe methods of diagnosing neuromuscular complications in critically ill patients and to appreciate advantages and limitations of different methods.
- To be able to list the differential diagnosis of ICUAW.

4

4.1 Introduction

Acute neuromuscular complications are common during critical illness, particularly among the most severe intensive care unit (ICU) patients with prolonged stay and mechanical ventilation, and those developing sepsis and multiple organ dysfunctions [1]. Lung, kidney, brain, and the circulatory and coagulation systems are traditionally reported as the most common failing organs, but no organ is spared by the devastating inflammatory response, and peripheral nerves and muscles are no exception [2].

Critical illness polyneuropathy (CIP) and myopathy (CIM) are the most common neuromuscular alterations encountered in the critically ill patient. Muscle deconditioning is also extremely common and often coexists with CIP and CIM [3]. These conditions may cause significant weakness developing after the onset of critical illness and are often indistinguishable clinically. Hence, electrophysiological investigations (EPS) of peripheral nerves and muscles are essential to define the pathological nature of weakness. CIP is a distal axonal neuropathy involving both motor and sensory nerves, and can be easily detected with nerve conduction study in the ICU, though differentiation with CIM is more complicated. Nerve biopsy is rarely if ever indicated; however, skin biopsy is minimally invasive and can be useful to assess histologically the tiny nerve fibers of the skin, which are often simultaneously involved. CIM is a primary myopathy, that is not secondary to muscle denervation, and can be diagnosed with nerve conduction study and electromyography (EMG). Proper diagnosis of myopathy requires that the patient collaborates to the EPS study. Alternatively, specialized neurophysiological techniques may be used to demonstrate altered muscle membrane excitability. Moreover, CIM includes various subtypes—from thick filament myopathy to necrotizing myopathy—that can be distinguished based on histological examination of muscle biopsy and that may have different prognosis. Therefore, muscle biopsy can be indicated to define the prognosis in uncertain cases. Lastly, muscle deconditioning due to immobility is associated with normal finding at EPS and disuse atrophy at muscle biopsy. Specific diagnosis would be important, as response to mobilization and prognosis can be better than with CIP or CIM. CIM and CIP may have a rapid onset and may resolve completely in a matter of weeks. However, in some survivors of critical illness, weakness may persist for months or years after discharge from hospital, and can be responsible for severe chronic physical disability.

This chapter reviews the history and the major clinical, electrophysiological, and histological features of CIP and CIM.

4.2 Historical Review

In 1984, Charles Bolton and his colleagues first described an acute polyneuropathy in critically ill patients who could not be weaned from the ventilator [4]. Patients had suffered from "adult" respiratory distress syndrome (as was called the "acute" respiratory distress syndrome at that time), pleural empyema complicating surgery, pneumonia, and lung abscesses. Despite the resolution of critical illness and interruption of sedative and analgesic drugs, "the patient could not tolerate a reduction in the frequency of mandatory mechanical ventilation" and was unable to breath spontaneously. The clinical signs included weak or absent spontaneous limb movements, weak grimacing of facial muscles, reduced muscle tone, and depressed deep tendon reflexes, suggesting a polyneuropathy. Electrophysiological study (EPS) of peripheral nerves and muscles and necropsy findings defined the nature of this polyneuropathy to be sensory-motor axonal degeneration. The authors described five patients in 4 years, so it seemed a very rare condition possibly due to "either a toxin or nutritional deficiency affecting only the peripheral nervous system." In 1986, the authors demonstrated that "critically ill polyneuropathy," as the condition was called at that time, was an entity distinct from the Guillain–Barré syndrome [5]. In 1987, the authors demonstrated that the "critical illness polyneuropathy" (CIP), a term suggested by P.K. Thomas, the editor of *Brain*, [6] was a distal, axonal, sensory-motor polyneuropathy complicating sepsis and multiple organ failure (MOF) [7]. CIP was no longer considered a disturbance affecting only the peripheral nervous system. The mechanism put forward was "a fundamental defect, still unknown, which causes dysfunction of all organ systems in this syndrome."

Muscle wasting may have always accompanied sepsis. However, before the support of respiration and circulation in ICUs, death usually occurred before the neuromuscular signs were clinically evident [8]. The story of CIM probably started in 1977 when MacFarlane and Rosenthal reported the case of a young asthmatic women developing diffuse muscle weakness after an acute respiratory failure requiring mechanical ventilation and a large dose of steroids [9]. After 8 days, the patient was unable to breathe spontaneously and to lift her limbs against gravity. Cranial nerves, deep tendon reflexes, and sensation were normal. Diagnosis of myopathy was based on electromyography, and the cause was attributed to the large doses of corticosteroids used to treat asthma. In 1979, Sher reported the first case of acute myopathy with extensive and selective loss of myosin (thick) filaments [10], which is now considered a common finding on muscle biopsy in milder forms of CIM [1]. In 1985 and then in 1991, Op de Coul et al. described a series of 22 patients, of whom 16 had EPS revealing neurogenic changes [9], myogenic changes [4], or combined neurogenic and myogenic changes [3] that the authors described as critical illness polyneuromyopathy [11]. In 1991, Witt showed that hyperglycemia together with hypoalbuminemia and prolonged ICU stay strongly correlated with development of CIP [12]. Following research on intensive insulin treatment will take advantage of this result, showing a substantial reduction of CIP in patients treated with higher doses of insulin to maintain normoglycemia [13, 14]. In the same year, Helliwell described muscle necrosis in 15 of 31 critically ill patients as a characteristic finding of the more severe forms of CIM [15], a result later confirmed by Ramsay [16]. In 1994, Zochodne described 7 patients developing an "acute necrotizing myopathy of intensive care," seemingly triggered by neu-

romuscular blocking agents [17]. In 1996, Latronico studied 24 acutely ill comatose patients developing severe muscle weakness or paralysis after the acute phase [18]. At the time of diagnosis 27 days after ICU admission, all patients had suffered from sepsis and multiple organ dysfunction or failure and were tetraplegic or had only minimal movements to painful stimulation. EPS indicated an acute, axonal polyneuropathy in all cases. Nerve biopsy, surprisingly, showed normal nerve in 14 patients and severe axonopathy in 8 patients. This discrepancy between EPS and histological nerve findings was seen in patients who had early biopsy, while all but 2 patients with late biopsy had agreement between EPS and histological findings. The authors hypothesized that "sepsis-related nerve failure caused an early impairment of axonal transport and transmembrane potential, a finding easily documented by electrophysiological but not by histological studies." Only with persisting sepsis, "the energy supply or use is not restored and histological alterations ensue." Muscle biopsy showed scattered muscle necrosis in 11 patients (48%), indicating that a primary myopathic process, that is not secondary to muscle denervation, was highly prevalent. The study also showed that CIP and CIM often coexist, and their combination probably is the most common manifestation of acute neuromuscular weakness in the ICU, a result that has been confirmed in following studies (see the supplementary material of reference [19] for Review).

4.3 The Clinical Diagnosis

The distinctive feature of CIP and CIM, alone or in combination, is generalized and symmetrical muscle weakness involving the respiratory muscles and the limbs [20]. Patients have different degrees of limb muscle weakness and are dependent on a ventilator, but facial muscles are usually spared such that facial grimace is preserved. This condition is currently defined as ICU-acquired weakness (ICUAW) and is typically described as a complication of critical illness [20–22]. In fact, ICUAW represents the extreme end of a spectrum of weakness that begins with any serious illness, regardless of care location [22].

The generalized muscle weakness caused by CIP, CIM, or pure muscle deconditioning is clinically indistinguishable [3, 23]. Proximal muscle groups are more affected than distal muscle groups [20, 24]. In CIM, sensory testing reveals normal sensation. However, sensory testing can be unreliable in the acute stage of disease, and CIM often coexists with CIP, making it difficult to differentiate CIP and CIM based on clinical criteria. CIM has as a better prognosis than CIP [46, 47], and hence pursuing differential diagnosis can be clinically relevant.

ICUAW is common, and recent data indicate that 40% of ICU patients (95% confidence interval, CI, 38–42%) may be affected [25]. Incidence is lower with clinical evaluation (95% CI, 30–35%) than with electrophysiological diagnostic techniques (95% CI, 45–50%). Patients with sepsis and prolonged mechanical ventilation are at particular high risk of developing ICUAW [26]. ICUAW is an important complication causing prolonged mechanical ventilation, lengthy ICU stay, and increased ICU and long-term mortality. This comes as no surprise considering that reduced muscular strength, as measured by grip strength, has been associated with an increased risk of all-cause and cardiovascular mortality in the general population [27].

A diagnosis of ICUAW is achieved by manually testing strength of 12 muscle groups using the Medical Research Council (MRC) scale or by measuring handgrip strength with a dynamometer. MRC sum score below 48/60 designates ICUAW or significant

weakness [20, 21], and an MRC score below 36/48 indicates severe weakness [24]. Recently, a simplified version of the scale with only four categories and improved clinimetric properties was proposed [28]. To date, this version has been validated in a small cohort of 60 critically ill patients with excellent inter-rater reliability and high sensitivity and specificity in diagnosing ICUAW compared to the full MRC [29]. Handgrip dynamometry measures isometric muscle strength and can be used as a quick diagnostic test. Cut-off values of less than 11 kg (IQR 10–40) in males and less than 7 kg (IQR 0–7.3) in females are considered to be indicative of ICUAW [30]. Inter-rater reliability of these two methods is good [31], but 25% of patients are not able to comply with clinical evaluation of ICUAW because MRC and handgrip dynamometry are volitional tests [25] and require the patients to be alert, cooperative, and motivated. Sedation, delirium, coma, pain, and injury often interfere with early clinical evaluation of muscle strength and accurate sensory and motor testing in the ICU [32–34] or patients are discharged early from the ICU before muscle strength can be assessed [35], and hence, ICUAW remains underreported. Recently, a neurophysiological technique has been proposed to assess the ankle dorsiflexor muscle force generated by tetanic 100 Hz electrical stimulation of the peroneal nerve [36]. With this method, muscle force production is measured also in non-cooperative patients and may be used as a non-volitional proxy of global muscle strength.

Accompanying respiratory weakness may be present in up to 80% of patients with ICUAW [37]. In patients undergoing a first spontaneous breathing trial, diaphragm dysfunction can be more frequent than limb muscle weakness [38]. Diaphragm dysfunction, which is associated with poor outcomes, can be evaluated in cooperative patients by measuring the maximal inspiratory pressure generated during a maximal inspiratory maneuver against an occluded airway [39]. However, results are strongly dependent on actual maximal performance of the effort. Alternatively and effort independent, changes in endotracheal tube pressure (twitch tracheal pressure) induced by bilateral anterior magnetic phrenic nerve stimulation (BAMPS) during airway occlusion (a pressure < 11 cmH_2O defines diaphragm dysfunction) [38] can be used. Diaphragm ultrasonography is also a useful technique with thickening fraction (end-inspiration thickness minus end-expiration thickness dived by end-expiration thickness) of less than 30–36% and the maximal diaphragmatic excursion below 10–14 mm defining dysfunction [40].

Weakness of the pharyngeal and laryngeal muscles and of the expiratory muscles of the chest wall and abdomen leads to altered swallowing, impaired cough, inadequate clearance of secretions, and increased risk of pulmonary aspiration and pneumonia.

Weakness of the pharyngeal and laryngeal muscles is common in critically ill patients surviving the acute event and may cause swallowing dysfunction (dysphagia). This is a serious and often underestimated complication of critical illness that, together with weakness of the expiratory muscles of the chest wall and abdomen, may impair cough and cause inadequate clearance of secretions and increased risk of pulmonary aspiration and pneumonia. Aspiration pneumonia is one of the most common causes for recurrent hospitalization in the 90 days after sepsis [22]. Conservative estimates indicate that 20% of all extubated survivors of acute respiratory failure suffer from an abnormality in swallowing function that may persist for several days to weeks [41]. Assessment of dysphagia is therefore recommended. If the patient is alert and able to maintain a sitting position, the water swallow test can be used as a screening test at the bedside [42]. Observation of a behavioral airway response, such as coughing, choking, throat clearing, or change in voice, is

highly suggestive of an ICU-acquired swallowing function, particularly after repeated testing, and should prompt specialist consultation for a more comprehensive diagnostic evaluation such as a videofluoroscopic swallow study or a fiberoptic endoscopic evaluation of swallowing [42].

Small fiber pathology with degeneration of tiny nerve fibers of the skin has also been described in critically ill patients [43]. Clinical presentation includes negative and positive sensory alterations, such as severe neuropathic pain or, respectively, absent or reduced pain and temperature sensation. Autonomic dysfunction can be present causing abnormal sweating, lacrimation and/or salivation; gastrointestinal, bladder, and sexual disorders; and orthostatic hypotension. The finger wrinkling test can be recorded after immersion of the right hand in a bucket filled with water at 40 °C and used to investigate sympathetic peripheral dysautonomia [43]. The degree of skin wrinkling at the fingertip is then assessed at baseline and after 5, 15, and 30 min, and graded using a 5-point clinical scale with score of 0 (absent wrinkling) to 2 (two or less lines of wrinkling are seen) indicating peripheral dysautonomia. Quantitative sensory testing (QST), a non-invasive method and psychophysical test, can be used to assess the functional impairment of sensory nerves [44]. By using standardized methods, abnormal thermal and pain detection thresholds can be revealed in significant proportions of critical illness survivors [45].

4.4 The Electrophysiological Diagnosis

ICUAW can be due to CIP and CIM alone or in combination, or due to pure muscle deconditioning with disuse atrophy. Comprehensive EPS are important to define the nature of the ongoing pathological process in patients with ICUAW. These studies should include motor and sensory nerve conduction studies as well as needle electromyography (EMG) in upper and lower limbs. With muscle deconditioning, the electrophysiological investigations (EPS) of peripheral nerves and muscles remain normal, whereas in CIP and CIM, EPS can identify the ongoing pathological process and will be reviewed afterward. EPS also carry long-term prognostic information [46–49].

4.4.1 Critical Illness Polyneuropathy

CIP is a distal axonal sensory-motor polyneuropathy, and hence nerve myelin sheaths are preserved (Fig. 4.1a). Conduction studies show normal or mildly reduced nerve conduction velocity, whereas the amplitudes of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) are reduced or nerves are completely unexcitable (Fig. 4.1b). Fibrillation potentials and positive sharp waves are recorded in the majority of patients with CIP but can be seen also in patients with CIM [50], reflecting muscle membrane irritability due to the inflammation or necrosis [51]. Therefore, they are useful to identify an abnormal process involving the neuromuscular system but cannot distinguish between CIP and CIM.

Using direct muscle stimulation [52, 53], a patient with CIP will have normal action potential amplitude when stimulating the muscle directly (dmCMAP) and reduced or absent CMAP when using conventional stimulation (i.e. through the motor nerve, neCMAP), rendering a neCMAP/dmCMAP ratio of less than 0.5 (the ratio will be zero if the neCMAP is absent) (Fig. 4.2) [1, 48, 54].

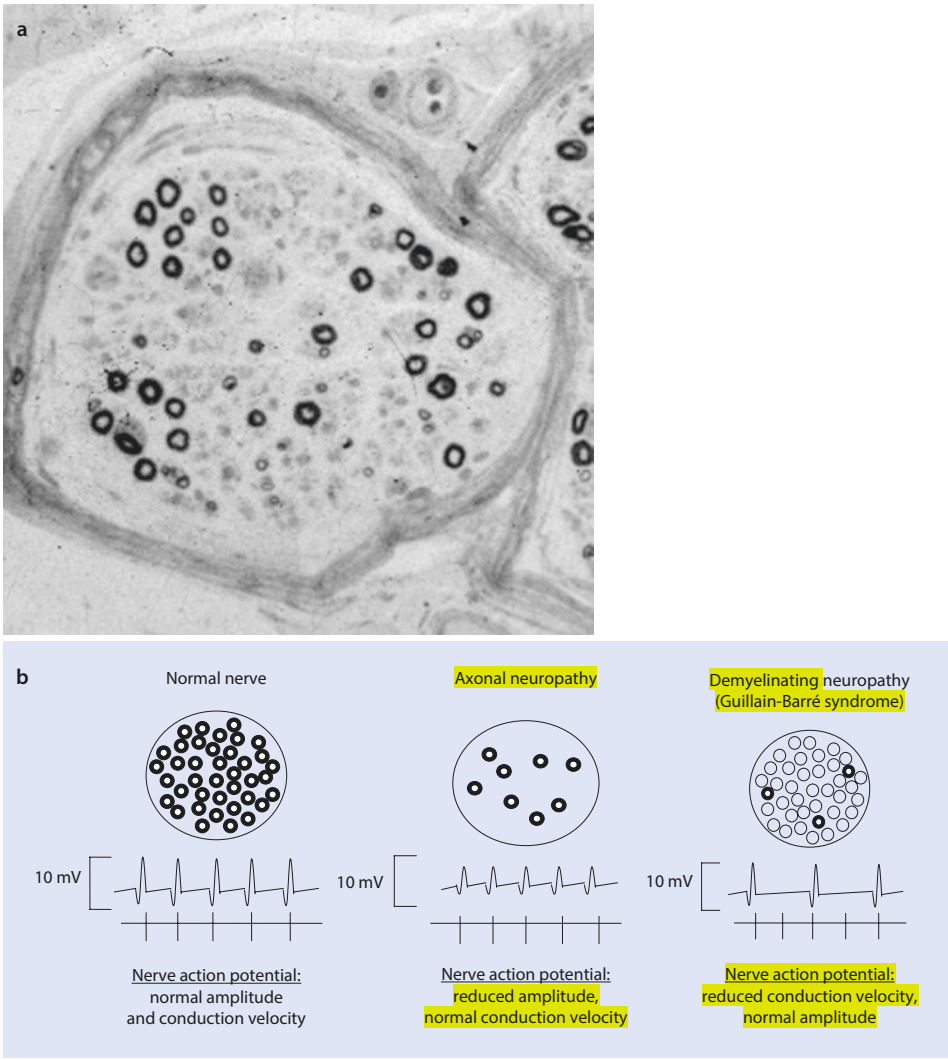


Fig. 4.1 **a** Light microscopic image of sural nerve biopsy showing axonal degeneration with decreased density of myelinated fibers, magnification ×150. (From Latronico and Bolton [1]). **b** Schematic presentation of axonal and demyelinating neuropathy. In axonal neuropathy, the total number of fibers is reduced, and hence the nerve action potential amplitude is reduced. Surviving fibers have normal myelin sheath; therefore, the nerve conduction velocity remains within normal limits. (From Latronico et al. [33])

4.4.2 Critical Illness Myopathy

EMG can easily identify CIM if the patient can collaborate to the EPD study. Voluntary contraction typically reveals rapid recruitment of low amplitude, short duration, polyphasic motor unit potentials. Moreover, SNAPs are normal. However, things are more complicated in real ICU life. First, in many instances, the critically ill patient has limited

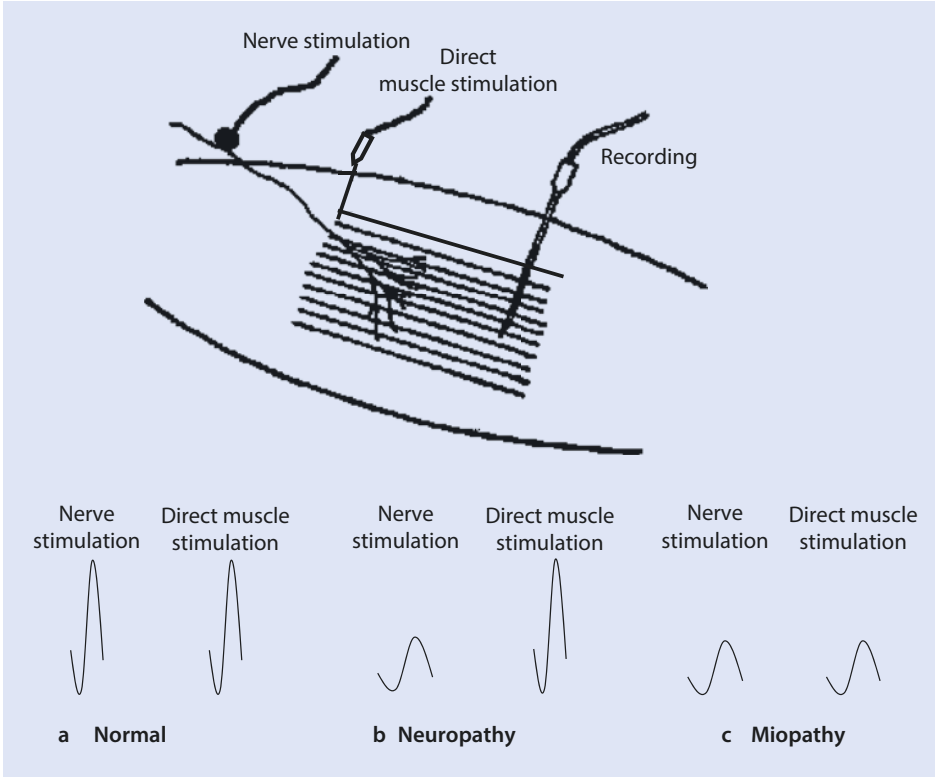


Fig. 4.2 Direct muscle stimulation. With this technique, in case of myopathy, the action potential will be reduced or absent after conventional stimulation through the nerve and direct muscle stimulation. (From Latronico et al. [33])

voluntary activity, which makes analysis of motor unit potential difficult. Second, patients may have limb edema precluding an accurate detection of SNAPs (SNAP amplitudes are measured in μV and are 1000 times smaller than cMAP amplitudes that are measured in mV). Third, CIM and CIP often coexist. In difficult cases, specialized neurophysiological techniques may help to differentiate CIM from CIP. Using direct muscle stimulation, a patient with CIM will have proportionally reduced or absent action potential amplitude after both conventional stimulation and DMS and the neCMAP/dmCMAP will be around 1. Likewise, a muscle action potential amplitude of less than 3 mV—normal values are above 3.0–3.2 mV [48, 55]—indicates a myopathy. CMAP has prolonged duration in CIM, probably as a consequence of impaired excitability and conductance of the muscle membrane and sodium channel dysfunction [50]. If accompanied by severe decrease in amplitude, prolongation of CMAP is highly suggestive of combined CIP and CIM [56], approaching 100% specificity when CMAP prolongation is found in more than 1 nerve [56]. In pure muscle deconditioning and atrophy caused by immobility, EPS usually show normal findings which represent an important criterion in the diagnostic and prognostic work-up since muscle deconditioning has a better prognosis than CIP or CIM (Fig. 4.4) [1, 3, 23].

4.4.3 Phrenic Nerve and Diaphragm

EPS of the phrenic nerve and the diaphragm may be helpful to identify diaphragm weakness as a contributor weaning failure. Phrenic nerve conduction studies and needle EMG of the respiratory muscles may establish CIP as the cause of failure to wean from the ventilator; however, these studies are rarely done in the acute setting. Diaphragm CMAPs can be recorded using surface electrodes; however, measurements are difficult to obtain because of electrical contamination from other respiratory muscles, the movements of the diaphragm during ventilation, the small amplitude of diaphragm CMAPs, and electrical interference in the ICU environment [57]. Diaphragm CMAP amplitudes can be recorded using commercially available esophageal electrodes used with neurally adjusted ventilator assist (NAVA), a new mode of mechanical ventilation in which diaphragm EMG is used to drive the ventilator. CMAP amplitudes recorded with the NAVA probe are higher than with surface electrodes which can facilitate recordings. These amplitudes tightly correlate with pressure generated by the diaphragm, but clear reference ranges are not available yet [58].

4.5 The Histological Diagnosis

4.5.1 Critical Illness Polyneuropathy

Autopsy studies have confirmed the electrophysiological findings of a primary distal axonal degeneration of motor and sensory fibers. In addition to peripheral nervous system involvement, chromatolysis of anterior horn cells has been demonstrated, indicating damage to the cell body axon [7].

Muscle biopsy in CIP shows evidence of acute denervation of muscle with atrophy of both type 1 and type 2 fibers. During the recovery phase, muscle biopsy will show grouped atrophy of the muscle fibers. Nerve biopsy will show signs of distal axonal degeneration if done later in the course of critical illness (Fig. 4.1) [18], but it is not indicated in clinical practice.

In addition to large nerve fiber damage, degeneration of somatic and autonomic epidermal and dermal small nerve fibers can be revealed by skin biopsy (Fig. 4.3) [43, 59, 60]. Degeneration of somatic epidermal nerve fibers in critical illness survivors is non-length dependent, suggesting that critical illness may affect the dorsal root ganglion neurons [43].

4.5.2 Critical Illness Myopathy

Muscle biopsy can be important to demonstrate the type and severity of the myopathic process and can be considered in ICUAW cases of uncertain prognosis (Fig. 4.4). Disruption of myofiber ultrastructure (Fig. 4.5a) is caused by decreased synthesis and increased degradation of myosin heavy chain [61, 62] and is an early event [62, 63] followed by myofiber atrophy at later stage (Fig. 4.5b). The term thick filament myopathy describes the selective loss of myosin "thick" filaments, which is a common histopathological feature in CIM and portends a good prognosis [1]. The pathological process pref-

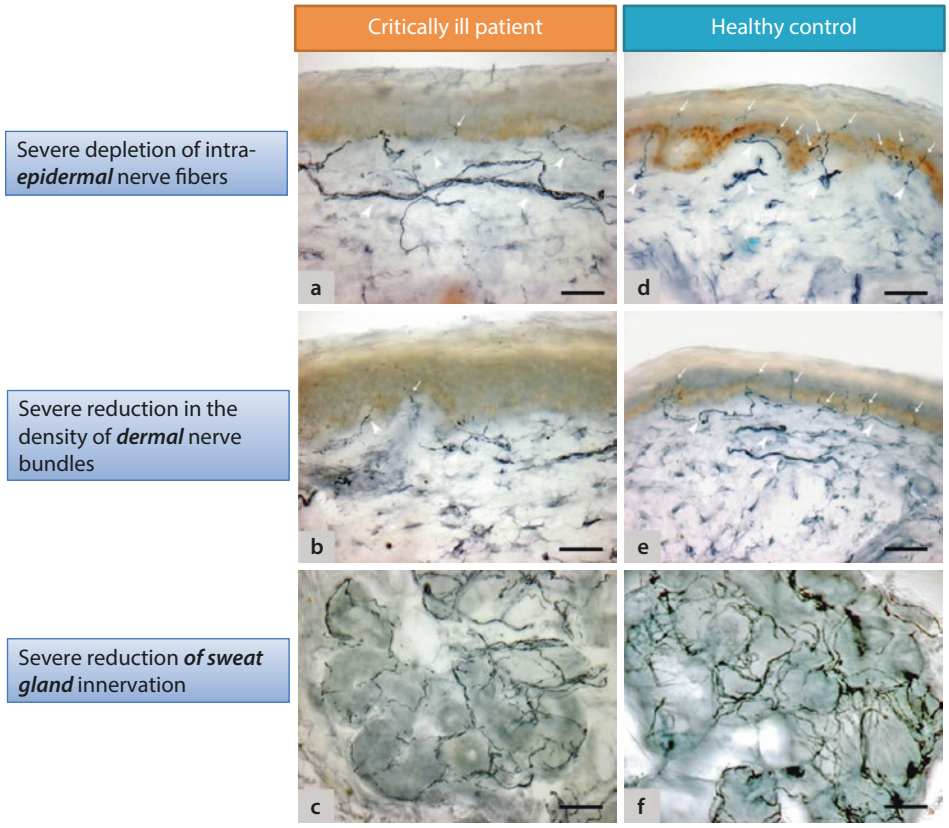


Fig. 4.3 Skin biopsy taken at the proximal thigh **a** and distal site of the leg **b** with a sweat gland **c** in patient no. 7, and at the proximal thigh **d** and distal site of the leg **e** with a sweat gland **f** in a healthy subject. Arrows indicate intra-epidermal nerve fibers and arrowheads indicate dermal nerve bundles. (From Latronico et al. [43])

erentially affects the myosin filaments resulting in decreased or absent reactivity in myofibrillar ATPase staining at light microscopy (Fig. 4.5b) and loss of thick filaments with disorganized myofibrils (Fig. 4.5a) and thinning of the A-bands at electron microscopy. Quantitative electrophoretic determination of the myosin content on percutaneous muscle biopsy specimens shows a decreased myosin/actin ratio [64]. Scattered muscle fiber necrosis can be observed in 40% of patients (Fig. 4.5c) [18, 22, 63] and has a worse prognosis than thick filament myopathy. In rare cases, an acute necrotizing myopathy with myofiber necrosis involving up to 95% of muscle fibers is described [15, 16]. Muscle atrophy mainly affecting type 2 fibers is a common finding, and in some cases, it is the only histopathological abnormality seen on muscle biopsy. Type II muscle fiber atrophy can also be associated with muscle unexcitability at direct muscle stimulation [65].

4.5.3 The Differential Diagnosis

The finding of generalized weakness is extremely common in critically ill patients and warrants an accurate differential diagnosis [66]. ICUAW is a diagnosis of exclusion, and clinical diagnosis is established if no alternative cause is found. Although clinical detection of

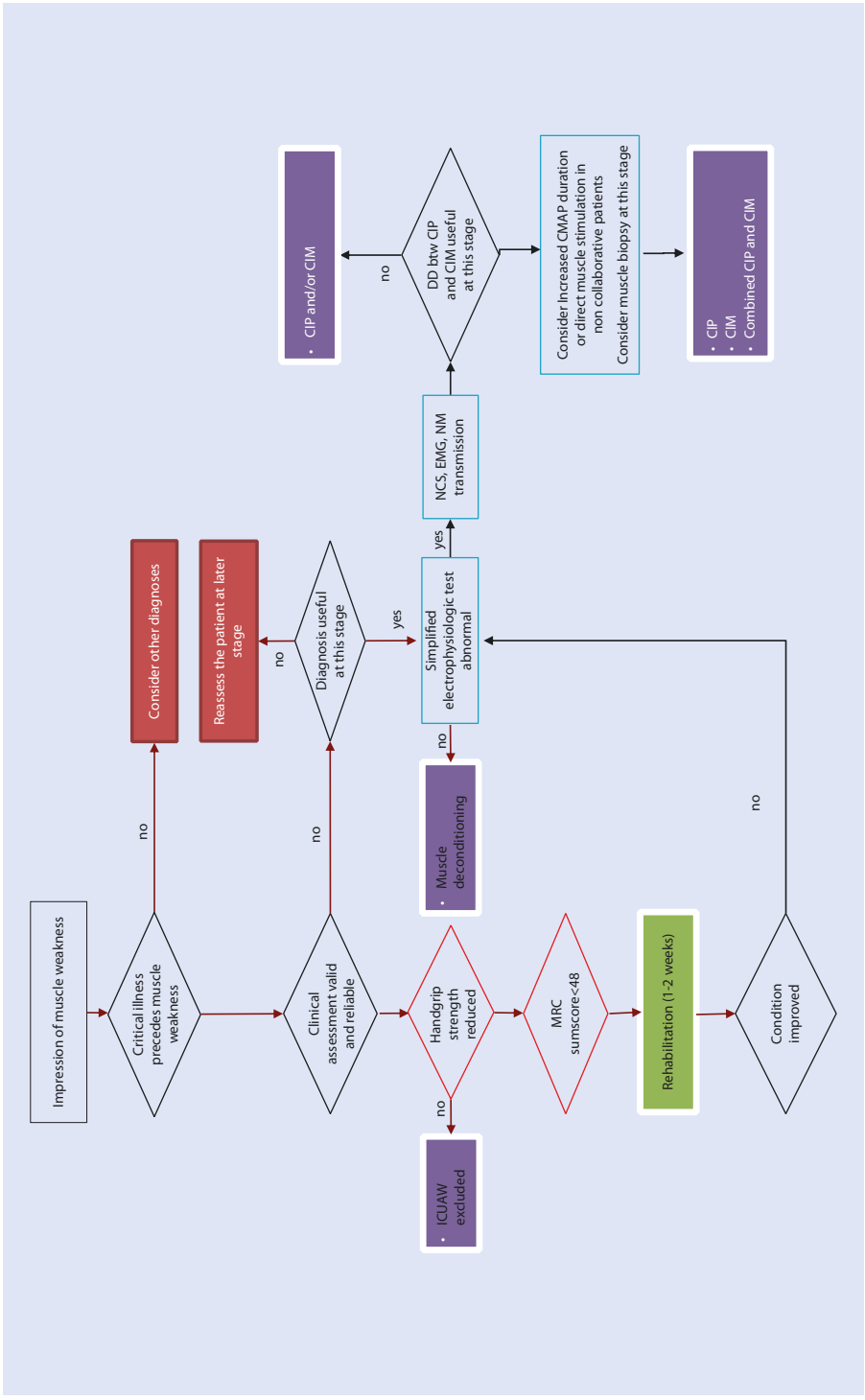


Fig. 4.4 Diagnostic algorithm for intensive-care-unit-acquired muscle weakness. (From Latronico and Gosselink [30])

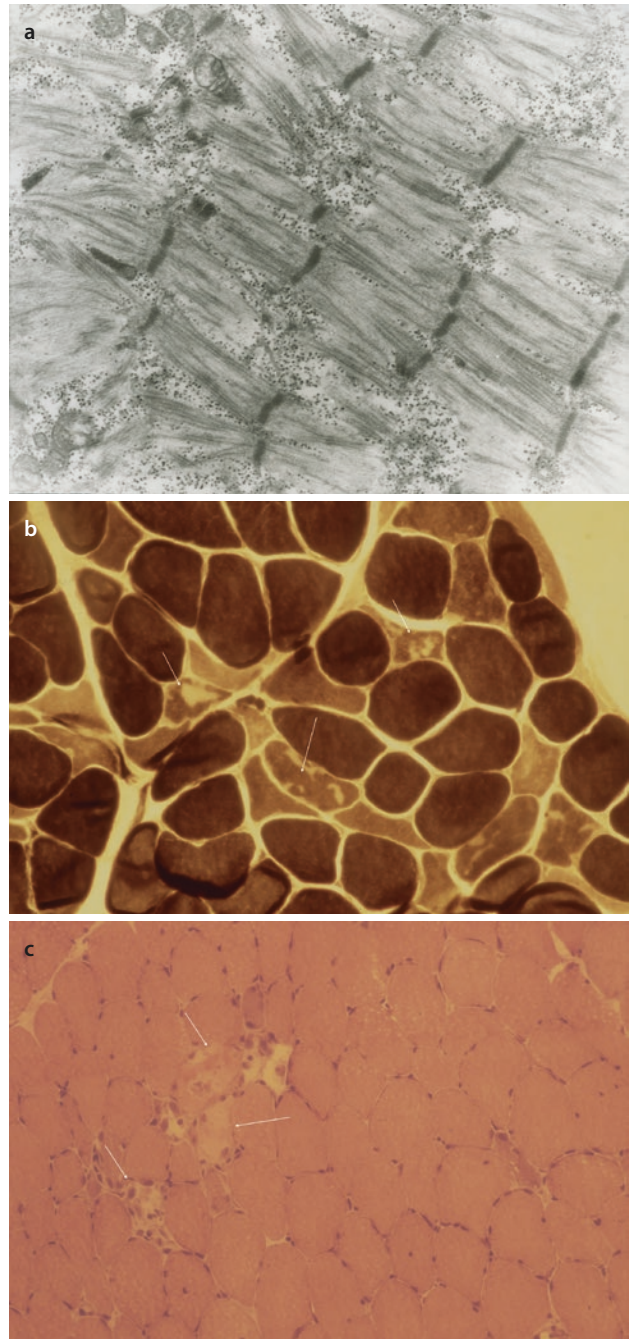


Fig. 4.5 Major histopathologic features of CIM. **a** Electron microscopy: myofibrils devoid of thick filaments with preserved Z lines (original magnification ×12 000); **b** hematoxylin eosin: necrotic muscle fibers (arrows) (original magnification ×20); **c** ATPase pH 4.6: muscle fiber atrophy (mainly type II) and focal loss of reactivity indicating loss of myofilaments (arrows) (original magnification ×40)

muscle weakness can be difficult in the acute stage of critical illness, as an initial observation, painful stimulation can cause facial grimacing with reduced or absent movement of the limbs [8]. Moreover, ICUAW is usually excluded in the presence of the following: the neurologic assessment indicates a brain disease (i.e. Babinski signs); facial muscles are involved (i.e. weakness of extraocular muscles with diplopia); muscle weakness is asym-

metrical (i.e. monoparesis or hemiparesis); progression of muscle weakness suggests a specific diagnosis with an ascending (Guillain–Barré syndrome) or descending pattern (botulin intoxication), or muscle weakness is fluctuating and worsens after brief exercise indicating a neuromuscular transmission defect (myasthenia gravis) or improves after exercise indicating presynaptic neuromuscular defect (Lambert–Eaton syndrome); there are fasciculations indicating early lower motor neuron involvement as in amyotrophic lateral sclerosis or associated abnormalities such as skin rash or abdominal pain pointing to dermatomyositis, vasculitis, porphyria, or diabetes; there are dysautonomic signs (i.e. dilated pupils poorly reactive to light suggesting botulin intoxication, and cardiac arrhythmias or fluctuations in blood pressure as seen in GBS); and pharmacological side effects are suspected (i.e. after prolonged administration of neuromuscular blocking agents, steroids, or cancer chemotherapy) (see [66] for review).

Once diagnosis of ICUAW is established, identification of underlying pathology requires neurophysiological and muscle biopsy studies (◘ Fig. 4.4) [30].

Conclusions

The neuromuscular system is one of the organ systems frequently affected by critical illness. The clinical manifestation of its involvement is labeled ICU-acquired weakness and affects peripheral as well as respiratory muscles. Muscle weakness during critical illness can originate from a primary neurogenic or a myogenic problem—labeled as critical illness polyneuropathy and critical illness myopathy—or a combination of both. ICUAW exposes patients to increased risk for delayed weaning from mechanical ventilation, as well as prolonged ICU and hospital stay but even compromises long-term outcomes. Differentiating between underlying pathological entities is clinically impossible but may be important as prognosis in terms of recovery rate and completeness of recovery, which tends to be better in pure CIM as compared to CIP or CIP/CIM. In cooperative patients who are not completely paralyzed, this can be achieved by nerve conduction studies and electromyography during voluntary contraction, assessing recruitment of motor unit potentials. In unconscious patients, alternative methods include the duration of CMAP or sophisticated tests comparing amplitudes elicited by nerve and direct muscle stimulation. Muscle biopsy may be considered in case of diagnostic uncertainty or to better estimate prognosis in cases of poor clinical progression. A variety of changes may be identified, including muscle fiber atrophy, selective loss of myosin, and fatty infiltration to overt muscle necrosis, with the latter carrying worse prognosis.

Take Home Messages

- Neuromuscular complications are common in critically ill patients and are considered to be the neuromuscular manifestations of multiple organ failure. Patients with sepsis and prolonged mechanical ventilation are particularly at risk.
- Neuromuscular complications may result from neuropathic alterations (CIP), myopathic alterations (CIM), or a combination of both. Associated muscle deconditioning is common.
- CIP and CIM are clinically indistinguishable. Typical features include generalized and symmetric weakness of the limbs and respiratory muscles. Cranial nerves and facial muscles are generally spared. Accompanying weakness of pharyngeal and laryngeal muscles, small fiber neuropathy, and autonomic dysfunction are frequently present.

- Clinical diagnosis of ICUAW can be made at the bedside by manual muscle strength testing. Handgrip dynamometry can be used as a quick screening tool. Both tests require patient cooperation.
- Associated respiratory weakness can be evaluated by measuring MIP (effort dependent), endotracheal tube pressure generated by BAMPS (effort independent), or diaphragm ultrasonography. Screening of swallowing dysfunction includes water swallow test, video fluoroscopic swallow study, and fiber optic endoscopic evaluation.
- EPS can be used when (1) patient is not cooperative and diagnosis of neuromuscular complications is deemed important at that stage and (2) if clinical improvement stays out. EPS allow to identify the underlying pathological process, yielding prognostic information.
- Comprehensive EPS consisting of nerve conduction studies and electromyography may reveal reduced SNAPs (in CIP or edema), reduced CMAPs (in CIP or CIM) with virtually normal conduction velocity, and spontaneous muscle electrical activity (may be present in both CIP and CIM). Differentiation between CIP and CIM can be made by analyzing motor unit recruitment during voluntary contraction. Alternatively, CMAP duration (prolonged in CIM) or DMS can be used.
- EPS of the phrenic nerve and diaphragm are technically challenging in the ICU. CMAP amplitudes may also be recorded with NAVA probes.
- Nerve biopsy is very invasive and not clinically indicated. The histological correlate of CIP is axonal degeneration.
- Muscle biopsy allows to identify type and severity of the myopathic process. It is selectively indicated in case of diagnostic uncertainty and may provide prognostic information.

References

1. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10:931–41.
2. Latronico N, Tomelleri G, Filosto M. Critical illness myopathy. Curr Opin Rheumatol. 2012;24:616–22.
3. Moss M, Yang M, Macht M, Sottile P, Gray L, McNulty M, Quan D. Screening for critical illness polyneuromyopathy with single nerve conduction studies. Intensive Care Med. 2014;40:683–90.
4. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry. 1984;47:1223–31.
5. Bolton CF, Laverty DA, Brown JD, Witt NJ, Hahn AF, Sibbald WJ. Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry. 1986;49:563–73.
6. Bolton CF. The discovery of critical illness polyneuropathy: a memoir. Can J Neurol Sci. 2010;37:431–8.
7. Zochodne DW, Bolton CF, Wells GA, Gilbert JJ, Hahn AF, Brown JD, Sibbald WA. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain. 1987;110(Pt 4):819–41.
8. Bolton CF. Neuromuscular manifestations of critical illness. Muscle Nerve. 2005;32:140–63.
9. MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. Lancet. 1977;2:615.
10. Sher JH, Shafiq SA, Schutta HS. Acute myopathy with selective lysis of myosin filaments. Neurology. 1979;29:100–6.
11. Op de Coul AA, Verheul GA, Leyten AC, Schellens RL, Teepen JL. Critical illness polyneuromyopathy after artificial respiration. Clin Neurol Neurosurg. 1991;93:27–33.

12. Witt NJ, Zochodne DW, Bolton CF, Grand'Maison F, Wells G, Young GB, Sibbald WJ. Peripheral nerve function in sepsis and multiple organ failure. Chest. 1991;99:176–84.
13. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348–53.
14. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, Bruyninckx F, Van den Berghe G. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175:480–9.
15. Helliwell TR, Coakley JH, Wagenmakers AJ, Griffiths RD, Campbell IT, Green CJ, McClelland P, Bone JM. Necrotizing myopathy in critically-ill patients. J Pathol. 1991;164:307–14.
16. Ramsay DA, Zochodne DW, Robertson DM, Nag S, Ludwin SK. A syndrome of acute severe muscle necrosis in intensive care unit patients. J Neuropathol Exp Neurol. 1993;52:387–98.
17. Zochodne DW, Ramsay DA, Saly V, Shelley S, Moffatt S. Acute necrotizing myopathy of intensive care: electrophysiological studies. Muscle Nerve. 1994;17:285–92.
18. Latronico N, Fenzi F, Recupero D, Guarneri B, Tomelleri G, Tonin P, De Maria G, Antonini L, Rizzuto N, Candiani A. Critical illness myopathy and neuropathy. Lancet. 1996;347:1579–82.
19. Latronico N. Critical illness polyneuropathy and myopathy 20 years later. No man's land? No, it is our land! Intensive Care Med. 2016;42:1790–3.
20. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphael JC, Outin H, Bastuji-Garin S. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288:2859–67.
21. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, Ali NA, Sharshar T. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009;37(10 Suppl):299–308.
22. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, Iwashyna T, Arabi Y, Citerio G, Wesley Ely E, Hall J, Mehta S, Puntillo K, Van den Hoeven J, Wunsch H, Cook D, Dos Santos C, Rubenfeld G, Vincent JL, Van den Berghe G, Azoulay E, Needham DM. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med. 2017;43(9):1270–81.
23. Latronico N, Smith M. Introducing simplified electrophysiological test of peripheral nerves and muscles in the ICU: choosing wisely. Intensive Care Med. 2014;40:746–8.
24. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, Casaer MP, Wouters P, Gosselink R, Van Den Berghe G. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45:18–25.
25. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. J Intensive Care Soc. 2015;16:126–36.
26. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, Hopkins RO, Hough CL, Kress JP, Latronico N, Moss M, Needham DM, Rich MM, Stevens RD, Wilson KC, Winkelman C, Zochodne DW, Ali NA, Adults ATSCoI-aWi, American Thoracic S. An official American thoracic society clinical practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014;190:1437–46.
27. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R, Rahman O, Swaminathan S, Iqbal R, Gupta R, Lear SA, Oguz A, Yusoff K, Zatonska K, Chifamba J, Igumbor E, Mohan V, Anjana RM, Gu H, Li W, Yusuf S, Prospective Urban Rural Epidemiology Study I. Prognostic value of grip strength: findings from the prospective urban rural epidemiology (PURE) study. Lancet. 2015;386:266–73.
28. Vanhoutte EK, Faber CG, van Nes SI, Jacobs BC, van Doorn PA, van Koningsveld R, Cornblath DR, van der Kooi AJ, Cats EA, van den Berg LH, Notermans NC, van der Pol WL, Hermans MC, van der Beek NA, Gorson KC, Eurelings M, Engelsman J, Boot H, Meijer RJ, Lauria G, Tennant A, Merkies IS. Modifying the Medical Research Council grading system through Rasch analyses. Brain J Neurol. 2012;135:1639–49.
29. Parry SM, Berney S, Granger CL, Dunlop DL, Murphy L, El-Ansary D, Koopman R, Denehy L. A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care. 2015;19:52.
30. Latronico N, Gosselink R. A guided approach to diagnose severe muscle weakness in the intensive care unit. Rev Bras Ter Intensiva. 2015;27:199–201.
31. Vanpee G, Hermans G, Segers J, Gosselink R. Assessment of limb muscle strength in critically ill patients: a systematic review. Crit Care Med. 2014;42:701–11.

32. Leijten FS, Poortvliet DC, de Weerd AW. The neurological examination in the assessment of polyneuropathy in mechanically ventilated patients. Eur J Neurol. 1997;4:124–9.
33. Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. Curr Opin Crit Care. 2005;11:126–32.
34. Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. Crit Care. 2011;15:R43.
35. Connolly BA, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, Polkey MI, Moxham J, Hart N. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. Crit Care. 2013;17:R229.
36. Connolly B, Maddocks M, MacBean V, Bernal W, Hart N, Hopkins P, Rafferty GF. Non-volitional assessment of tibialis anterior force and architecture during critical illness. Muscle Nerve. 2018;57(6):964–72.
37. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, Albaladejo P, Chanques G, Molinari N, Jaber S. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42:853–61.
38. Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, Similowski T, Demoule A. Coexistence and impact of Limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med. 2017;195:57–66.
39. Supinski GS, Morris PE, Dhar S, Callahan LA. Diaphragm dysfunction in critical illness. Chest. 2018;153(4):1040–51.
40. Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. Intensive Care Med. 2017;43:29–38.
41. Macht M, White SD, Moss M. Swallowing dysfunction after critical illness. Chest. 2014;146:1681–9.
42. Brodsky MB, Suiter DM, Gonzalez-Fernandez M, Michtalik HJ, Frymark TB, Venediktov R, Schooling T. Screening accuracy for aspiration using bedside water swallow tests: a systematic review and meta-analysis. Chest. 2016;150:148–63.
43. Latronico N, Filosto M, Fagoni N, Gheza L, Guarneri B, Todeschini A, Lombardi R, Padovani A, Lauria G. Small nerve fiber pathology in critical illness. PLoS One. 2013;8:e75696.
44. Terkelsen AJ, Karlsson P, Lauria G, Freeman R, Finnerup NB, Jensen TS. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol. 2017;16:934–44.
45. Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W. Somatosensory functions in survivors of critical illness. Crit Care Med. 2017;45:e567–74.
46. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. JAMA. 1995;274:1221–5.
47. Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry. 2008;79:838–41.
48. Koch S, Spuler S, Deja M, Bierbrauer J, Dimroth A, Behse F, Spies CD, Wernecke KD, Weber-Carstens S. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. J Neurol Neurosurg Psychiatry. 2011;82:287–93.
49. Hermans G, Van Mechelen H, Bruyninckx F, Vanhullebusch T, Clerckx B, Meersseman P, Debaveye Y, Casaer MP, Wilmer A, Wouters PJ, Vanhorebeek I, Gosselink R, Van den Berghe G. Predictive value for weakness and 1-year mortality of screening electrophysiology tests in the ICU. Intensive Care Med. 2015;41:2138–48.
50. Goodman BP, Harper CM, Boon AJ. Prolonged compound muscle action potential duration in critical illness myopathy. Muscle Nerve. 2009;40:1040–2.
51. Paganoni S, Amato A. Electrodiagnostic evaluation of myopathies. Phys Med Rehabil Clin N Am. 2013;24:193–207.
52. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology. 1996;46:731–6.
53. Rich MM, Bird SJ, Raps EC, McCluskey LF, Teener JW. Direct muscle stimulation in acute quadriplegic myopathy. Muscle Nerve. 1997;20:665–73.
54. Weber-Carstens S, Koch S, Spuler S, Spies CD, Bubser F, Wernecke KD, Deja M. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients. Crit Care Med. 2009;37:2632–7.
55. Trojaborg W, Weimer LH, Hays AP. Electrophysiologic studies in critical illness associated weakness: myopathy or neuropathy--a reappraisal. Clin Neurophysiol. 2001;112:1586–93.

56. Kramer CL, Boon AJ, Harper CM, Goodman BP. Compound muscle action potential duration in critical illness neuromyopathy. Muscle Nerve. 2018;57(3):395–400.
57. Ackermann KA, Brander L, Tuchscherer D, Schroder R, Jakob SM, Takala J, Z'Graggen WJ. Esophageal versus surface recording of diaphragm compound muscle action potential. Muscle Nerve. 2015;51:598–600.
58. Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43:1441–52.
59. Skorna M, Kopacik R, Vlckova E, Adamova B, Kostalova M, Bednarik J. Small-nerve-fiber pathology in critical illness documented by serial skin biopsies. Muscle Nerve. 2015;52:28–33.
60. Axer H, Grimm A, Pausch C, Teschner U, Zinke J, Eisenach S, Beck S, Guntinas-Lichius O, Brunkhorst FM, Witte OW. The impairment of small nerve fibers in severe sepsis and septic shock. Crit Care. 2016;20:64.
61. Derde S, Hermans G, Derese I, Guiza F, Hedstrom Y, Wouters PJ, Bruyninckx F, D'Hoore A, Larsson L, Van den Berghe G, Vanhorebeek I. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med. 2012;40:79–89.
62. Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, Langhans C, Haas K, Radtke T, Kleber C, Spies C, Labeit S, Schuelke M, Spuler S, Spranger J, Weber-Carstens S, Fielitz J. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. 2014;40:528–38.
63. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Padhke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310:1591–600.
64. Stibler H, Edström L, Ahlbeck K, Remahl S, Ansved T. Electrophoretic determination of the myosin/actin ratio in the diagnosis of critical illness myopathy. Intensive Care Med. 2003;29:1515–27.
65. Bierbrauer J, Koch S, Olbricht C, Hamati J, Lodka D, Schneider J, Luther-Schroder A, Kleber C, Faust K, Wiesener S, Spies CD, Spranger J, Spuler S, Fielitz J, Weber-Carstens S. Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane. Crit Care Med. 2012;40:647–50.
66. Sharshar T, Citerio G, Andrews PJD, Chieregato A, Latronico N, Menon DK, Puybasset L, Sandroni C, Stevens RD. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. Intensive Care Med. 2014;40:484–95.

Neuromyopathy: Histological and Molecular Findings

Julius J. Grunow, Tobias Wollersheim, and Steffen Weber-Carstens

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_5

Learning Objective

After reading the chapter, the reader should be able to…

- Outline histological and molecular findings in muscle and nerves of critically ill patients
- Explain basic pathophysiological concepts that contribute to the observed histological and molecular changes in muscle and nerves of critically ill patients

5.1 Introduction

5

Critical illness myopathy and critical illness polyneuropathy describe the two underlying pathophysiological entities that lead to intensive care unit-acquired weakness (ICUAW).

"Rapid loss of flesh" was an observation made in 1892 in septic patients by William Osler and was simultaneously the first description of a pathological entity that would later be defined as critical illness myopathy (CIM) [1]. Over a century later, Latronico and colleagues were the first to objectify the observed atrophy as a defining characteristic of critical illness myopathy [2]. Meanwhile, Bolton and others were able to show in 1984 that critical illness polyneuropathy (CIP) is a primary neuropathy caused by axonal degeneration [3].

Since then, tremendous efforts have been undertaken by researchers to elucidate histological characteristics and molecular mechanisms of critical illness-associated failure of the neuromuscular organ system. A basic understanding of these concepts is important not only to the before-mentioned researchers who work on pathophysiological mechanisms and novel treatment approaches but also to physicians and nurses who are confronted with patients affected by failure of the neuromuscular organ system during their everyday routine. A substantial knowledge will help them to incorporate critical illness myopathy and critical illness polyneuropathy into their patient management decisions.

This chapter will outline important histological and molecular characteristics of critical illness myopathy and critical illness polyneuropathy as well as pathophysiological concepts leading up to these findings.

5.2 Molecular Pathology in CIM and CIP

Critical illness myopathy (CIM) frequently develops alone, while critical illness polyneuropathy (CIP) is for the most part observed in conjunction with CIM [4, 5]. A distinct pathophysiology can be observed in patients developing CIM as well as in patients developing CIP; however, when both evolve simultaneously, an overlap can be observed, named critical illness neuromyopathy (CINM).

5.2.1 Critical Illness Myopathy

Critical illness myopathy can be classified as an acute primary myopathy that diminishes muscle mass and impairs muscle function leading to clinically observable weakness and deteriorated outcome [2, 3, 6]. Even though in concomitant CIP, a neurogenic component of atrophy and muscle function impairment can be observed, the effect is additive and has no causal role in the development of CIM [3].

5.2.1.1 Muscle Homeostasis

Muscle homeostasis is the balance between muscle protein synthesis and muscle protein degradation. It is responsible for maintenance of muscle mass. Every imbalance independent of its nature—either physiologic or pathologic—leads to an increase or decrease in muscle mass. The nature of the imbalance determines if it is an adaptive or a maladaptive process. During critical illness, an imbalance in muscle homeostasis is observed, which leads to a maladaptive shift toward muscle protein degradation.

This shift is a result of insufficient muscle protein synthesis, as seen on mRNA level by depressed expression of genes encoding for myosin heavy chains as well as on protein level shown by a diminished fractional synthesis rate determined through the incorporation of labeled amino acids into the muscle [7–10]. The counterparts to the insufficient muscle synthesis are dysfunctional muscle degrading systems, which lead to increased protein breakdown [7, 8, 11]. One of them is the ubiquitin-proteasome system (UPS), which is mainly involved in degradation of myofibrillar components that are necessary for muscle force generation [12]. The UPS consists, among others, of E3-ligases—MuRF-1 and Atrogin-1—, which label proteins with ubiquitin in an ATP-dependent fashion. This labeling process sequentially enables the 26S proteasome, representing a proteolytic ATP-dependent complex consisting of a regulatory 19S subunit and a catalytic 20S subunit, to recognize proteins and degrade them into small peptides, which are subsequently further degraded by cytoplasmic exopeptidases [13]. During critical illness, mRNA expression as well as protein content of MuRF-1 and Atrogin-1 are significantly increased [8, 14, 15]. In synergy with a higher proteasome activity, these data show the involvement of the UPS in the disbalanced muscle homeostasis during critical illness [10, 15–18]. As recent trials indicate, the activation of the UPS is suspected to be triggered by inflammation [19, 20].

The other muscle protein degrading system is the autophagy system. It encompasses three different types: macroautophagy, microautophagy, and chaperon-mediated autophagy. Macroautophagy, whose main purpose is cellular housekeeping and degradation of dysfunctional organelles or misfolded proteins, is initiated by the formation of a double-membrane phagophore. This phagophore subsequently grows around the degradable substrate and fuses to form the autophagosome, which is then transported via the microtubule machinery to fuse with a lysosome, responsible for the actual degradation process. During critical illness, tight regulation of autophagy is essential. Both an overactivation with unphysiologically high protein degradation and a depression, which effectuates an accumulation of potentially toxic substrates, could be detrimental. Macroautophagy has been implicated to contribute to the neuromuscular organ dysfunction during critical illness, since skeletal muscle presents with a phenotype that is highly indicative of insufficient autophagy. This phenotype is defined by the observation of central nuclei and vacuolization of myofibers [21]. Corroborating this phenotype is on the one hand the low LC3II/LC3I ratio representing insufficient formation of the autophagosome and on the other hand the accumulation of substrates like p62 and ubiquitin, which are degraded during proper functioning of autophagy [21]. Furthermore, a decreased LC3II/LC3I ratio was observed in patients that demonstrated relevant muscle weakness underlining the importance of autophagy for the observed clinical phenotype [22].

5.2.1.2 Muscle Morphology

The consequence of these processes, which occur within the first week after ICU admission, is a severe skeletal muscle atrophy determined through a reduced myofiber cross-sectional area as well as a reduced muscle protein content [7–9, 18, 23].

Myofiber cross-sectional area declines between 1.5% and 13.2% per day depending on the different patient-associated factors and fiber type. On average, this results in a reduction of 17.5% until the seventh day after ICU admission and a reduction of up to 28% for type I, 42% for type IIa, and 32% for type IIb muscle fibers [7, 8, 24]. As ultrastructural changes on the sarcomere level can only be observed by electron microscopy, these numbers might be underestimated. Early during the course of illness, ultrastructural architecture of the sarcomeres is preserved, while myofilaments are already absent [8, 15, 18]. Besides reduction of total myofiber size, a reduction in myofiber density (myofiber cross-sectional area per defined muscle area) can be observed, indicating infiltration or remodeling processes within the muscle. Reduced myofiber density could be associated with the deposition of lipid droplets, proliferation of connective tissue represented by intrafascicular fibrosis or edema [2, 8, 10, 25] (Fig. 5.1).

As can already be abstracted from the previously shown data, predominance of atrophy in fast-twitch type II muscle fibers is characteristic for critical illness myopathy [8, 9, 15, 24, 26, 27]. Even though type II muscle fibers are more severely affected by atrophic processes, no change in muscle fiber distributions can be observed [15]. Another characteristic finding is the selective loss of thick filaments, meaning myosin filaments, which was established through electron microscopy as well as the absence of myofibrillar ATPase activity [18, 23, 26, 28]. This selective loss leads to a split appearance of the sarcomeric A-band, while the Z-band is preserved [23]. Muscle necrosis is another characteristic finding of critical illness myopathy and is observed in conjunction with macrophagocytosis [7, 25, 27, 29]. However, even though muscle necrosis is a common finding, reports indicate that it is neither always observable nor is it pathognomonic. Fiber-type grouping, as a sign of neurogenic atrophy and reinnervation, is usually not evident in CIM patients [26]. Due to the inflammatory nature of most diseases leading to a critical illness state and the association between inflammation and muscle degradation, it seems intuitive that inflammatory infiltrates are common within the muscle. Some studies corroborate this intuition, while others failed to do so [8, 29].

The involvement of glucocorticoids or neuromuscular-blocking agents (NMBA) in neuromuscular organ failure is an ongoing debate. Histological analyses show an overlap between Glucocorticoid-induced Myopathy and CIM, since they both feature predominant fiber type-II atrophy, but the extent to which glucocorticoids contribute is unclear [30]. Furthermore, a loss of thick filaments with preservation of the Z-bands, a reduced myofibrillar ATPase staining, and a severe atrophy without fiber type grouping was evident in a patient treated with NMBA and corticosteroids, which also hints toward the involvement of glucocorticoids and NMBA in the development of CIM [31]. Recent studies indicate that the overall role is of rather small magnitude, as most patients received glucocorticoids and NMBA at low dosages and that the observed effect is additive [10].

Denervation atrophy is not a characteristic feature of CIM. Nevertheless, in some patients, signs of denervation atrophy such as fiber type unspecific atrophy as well as fiber type grouping, target fibers, and central nuclei as signs of reinnervation were observed, which is attributed to the development of CIP in parallel to CIM and its independent effect on muscle tissue [2, 3, 26, 32, 33].

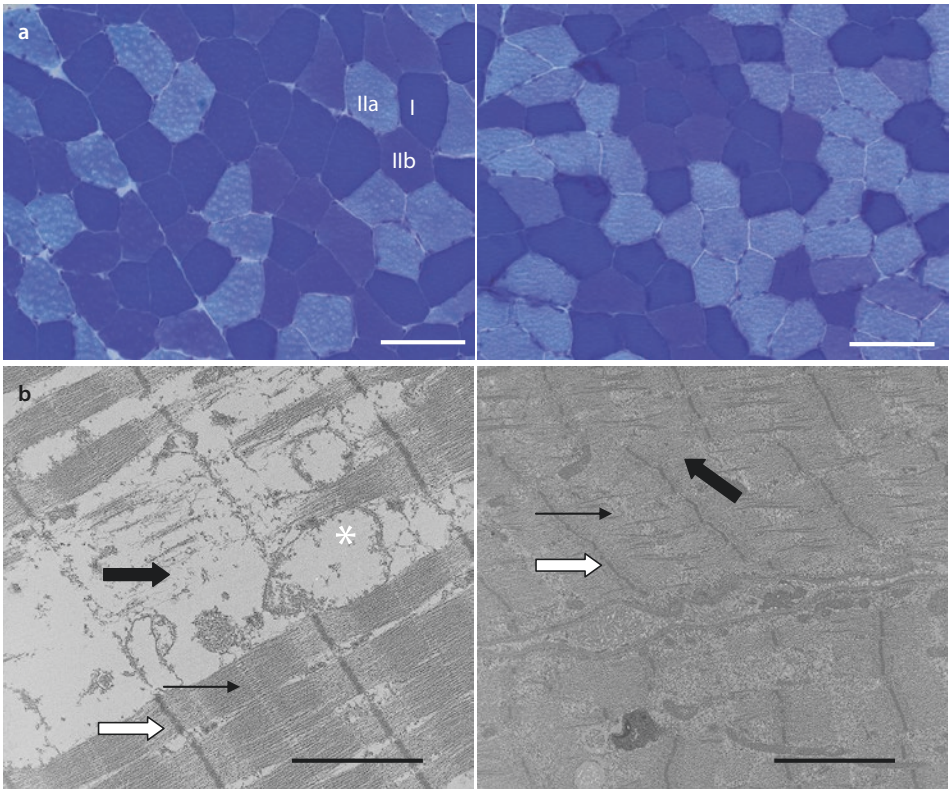


Fig. 5.1 Fast- and slow-twitch fibers atrophied during critical illness. **a** ATPase stained vastus lateralis cross-sections from critically ill patients 5 (left) and 15 (right) days after ICU admission (type-I, -IIa, and -IIb fibers are indicated; scale bar 100 μm). **b** Representative electron micrographs from vastus lateralis cross sections from critically ill patients 5 (left) and 15 (right) days after ICU admission showed that myofiber ultrastructure is destroyed early during critical illness (scale bar 2 μm). Myosin loss and mitochondrial ballooning also appeared early during critical illness (left). Fifteen days after ICU admission, myosin became squeezed and distorted, Z-lines were deformed, and H-zone shapes were blurred (right). Myosin loss (thick black arrow), Z-lines (white arrow), H-zone (small black arrow), and mitochondria (white star). (The figure and the caption are taken from Ref. [8])

The findings and concepts described above only address the acute phase of critical illness during the ICU stay. Since intensive care unit-acquired weakness has an impact on patients shown up to 5 years after discharge, the pathophysiological processes during rehabilitation after discharge from the ICU should not be disregarded.

After discharge from the ICU, histologic muscle atrophy was still evident in 100% of patients after 7 days. Even though muscle mass increased in all patients within 6 months, atrophy was still evident in 70%. Similar to the atrophy, the sarcomere architecture was destroyed in 100% of patients 7 days after discharge. Destruction, however, resolved in all patients within 6 months. UPS activity was also increased at 7 days after discharge, but this increase ceased to physiologic levels until 6 months after discharge. UPS activity was matched by an inflammatory infiltrate with leukocytes [34].

Take Home Message

Characteristic histologic findings of critical illness myopathy:
- Muscle fiber atrophy
- Predominance of type II muscle fiber atrophy
- Loss of thick filaments (Myosin)
- Absence of myofibrillar ATPase activity
- Necrosis (not necessarily)

Additional histologic findings of critical illness myopathy:
- Lipid droplets
- Denervation Atrophy (if CIP is also present)
- Intrafascicular fibrosis
- Edema
- Inflammatory infiltration

During critical illness, the correlation between muscle mass and muscle strength is abrogated, and even during recovery a regain of muscle mass does not necessarily coincide with a regain of muscle strength. This indicates a functional component to be involved in neuromuscular organ failure during critical illness [34, 35].

Muscle function is a complex synergistic process consisting of two main components: excitation and contraction. A disruption of either one of the parts as well as of the coupling could lead to contractile muscle dysfunction as observed during critical illness.

5.2.1.3 Mitochondrial Dysfunction

Muscle contraction is a highly energy-consuming process. We have an ATP turnover equivalent to our body weight every day. Metabolic derangements such as bioenergetic failure could therefore easily hamper muscle contraction. Mitochondria cover roughly 90% of the daily ATP requirements, which makes a mitochondrial dysfunction highly plausible as a causal factor for the contractile dysfunction observed in muscle during and after critical illness.

Mitochondrial content in skeletal muscle is reduced during critical illness, and remaining mitochondria are swollen with a decreased relative surface area shown in electron microscopy [36, 37].

ATP content and mitochondrial function influence the outcome of patients with septic shock. It was shown that impairment of mitochondrial function in skeletal muscle is caused by critical illness and leads to reduced ATP content and worsened outcome through reduced respiratory chain activity [38, 39]. The reduced capacity of mitochondria to produce ATP cannot solely be observed in muscle of septic patients but also in muscle of patients that develop relevant muscle weakness (MRC < 48). Survivors of sepsis show a compensatory response to impaired mitochondrial function in form of upregulated mitochondrial biogenesis and increased expression of respiratory chain complexes in skeletal muscle [39]. The induction of mitochondrial biogenesis also differentiates patients who develop CIM from patients who do not [40].

Oxidative stress is inherent to the inflammatory response in sepsis but is also thought to be involved in organ dysfunction. Enzymes such as the superoxide dismutase (SOD) protect the body from damage through oxidative stress. Mitochondria have their own

subtype of SOD, and patients who survive sepsis show an upregulation of this mitochondrial SOD in skeletal muscle. The upregulation represents an oxidative stress response protecting mitochondria from damage and probably sustaining proper functioning of mitochondria and muscle contraction [39].

The above-described reduction in mitochondrial content was evident 7 days after discharge from the ICU during recovery from critical illness. Six months after discharge from the ICU, this reduction in mitochondrial content was resolved showing that during recovery mitochondrial content increases [34].

5.2.1.4 Insulin Resistance

Contractile dysfunction as a result of insufficient energy supply cannot only evolve on the mitochondrial level. In order for the mitochondria to function properly, they have to be provided with the necessary substrates such as glucose via glycolysis.

Insulin resistance is a common finding during critical illness. Up to today, the exact pathomechanism of insulin resistance has not been elucidated. The uptake of glucose into muscle is both insulin-dependent and insulin-independent, in which case muscle contraction is the appropriate trigger for glucose uptake. In both cases, a translocation of GLUT4 channels into the sarcolemma is obligatory. Patients with CIM present an impaired insulin-dependent translocation of GLUT4 into the sarcolemma as seen in immunohistochemistry, which is in line with an increased systemic insulin resistance measured via insulin sensitivity index. Additionally, a key regulator of insulin-independent GLUT4 translocation - AMPK - is dysfunctional, impairing insulin-independent GLUT4 translocation. As a result, muscle tissue is deprived of glucose possibly contributing to the phenotype of CIM. In line with this hypothesis is the fact that type II muscle fibers would be more severely affected, since they are more dependent on glycolytic metabolism [40].

5.2.1.5 Non-Excitable Muscle Membrane

Decreased muscle membrane excitability is a characteristic finding in patients with critical illness myopathy [41, 42]. A non-excitable muscle membrane impairs excitation–contraction coupling, which is associated with muscle weakness. Preliminary results from research on cell culture and animal models explained membrane inexcitability through a depolarization of the resting potential and a shift of sodium channel inactivation into the hyperpolarized direction [43]. Both these change prevent a regular action potential transmitted at the neuromuscular junction on to the myofiber from reaching the threshold for a myofiber action potential, which in succession would lead to a muscle contraction. Due to a lack of trials in humans with critical illness myopathy, the exact pathogenesis and impact of sodium channel dysfunction on muscle membrane inexcitability remains unclear.

5.2.1.6 Ca^{2+}-Homeostasis

Calcium is the link between excitation and contraction during a process termed excitation–contraction coupling. After arrival of an action potential (AP) at the neuromuscular junction, it is transmitted on to the sarcolemma. The transmitted AP activates the dihydropyridine receptor that mediates Ca^{2+} influx through the opening of the ryanodine receptor calcium release channel. The rising Ca^{2+} concentration then triggers muscle contraction through binding of Ca^{2+} to Troponin C, that hampers muscle contraction if Ca^{2+} is not available. In order for the muscle contraction to cease, Ca^{2+} has to be quickly eliminated from the sarcoplasm. This process is mediated by the sarcoplasmic reticulum Ca^{2+}-ATPase. A tight regulation of Ca^{2+} levels is inevitable for proper muscle function.

Research on animal models indicates that Ca^{2+} plays an important role during the development of CIM and muscle membrane inexcitability. The role is underlined by the fact that fluctuation of Ca^{2+} plasma concentration is an important risk factor for the development of CIP/CIM [2, 32].

Take Home Messages

Key pathophysiological concepts of critical illness myopathy:

- Activation of the UPS system leads to severe muscle atrophy and causes CIM through reduction of muscle mass.
- Insufficient autophagy leads to accumulation of toxic substances and dysfunctional organs, which inhibit proper muscle function.
- Mitochondrial dysfunction is responsible for ATP depletion hampering muscle function through insufficient energy supply.
- Insulin resistance and insufficient GLUT4 translocation deplete muscle fibers of glucose and are involved in the pathophysiological mechanism of critical illness myopathy through an insufficient energy supply.
- A non-excitable muscle membrane caused by a depolarized resting potential or a shift of sodium channel inactivation into the hyperpolarized direction disables excitation–contraction coupling and muscle function.
- Disturbances within the Ca^{2+}-homeostasis cause critical illness myopathy through insufficient excitation–contraction coupling.

5.2.2 Critical Illness Polyneuropathy

Critical illness polyneuropathy is a primary axonal polyneuropathy that manifests in motor and/or sensory nerves [2].

Pathophysiologically, critical illness polyneuropathy can be divided into an early and a late phase since a discrepancy between manifestations of clinical symptom as well as electrophysiological changes and histologic alterations was observed. During the early phase (approximately first 2 weeks), nerve histology was without a pathologic finding while impaired nerve function could be shown during electrophysiologic examination. This discrepancy dissolved in the late phase of sepsis, when electrophysiologically impaired nerve function was matched by pathologic nerve histology findings [2].

5.2.2.1 Nerve Morphology

Histological manifestation of nerve pathology is aggravated distally. Since clinical manifestation of muscle weakness during critical illness is pronounced proximally, the finding during histologic analysis of peripheral nerves shows a discrepancy to the clinical manifestation [32, 33].

Characteristic finding during critical illness polyneuropathy is an axonal degeneration with a loss of myelinated fibers in peripheral motor and sensory nerves [2, 3, 33]. This loss also reflects in intraepidermal nerve fiber density, which was reduced in septic patients [44]. Due to the unclear pathophysiology of critical illness polyneuropathy are all these findings not pathognomonic. Less common and uncharacteristic findings are found not only in the peripheral nervous system but also in the central nervous system. These findings encompass the chromatolysis of anterior horn cells as well as loss of dorsal root ganglion cells [33].

Immune cell infiltration and demyelination are histologic alterations usually not observed during critical illness.

Take Home Message

Characteristic histologic findings of critical illness polyneuropathy:
- Axonal degeneration
- Loss of myelinated fibers
- Distal aggravation

Additional histologic findings of critical illness polyneuropathy:
- Chromatolysis of anterior horn cells
- Loss of dorsal root ganglion cells

5.2.2.2 Microcirculatory Insufficiency

Microcirculatory alterations are frequent during sepsis and have been implicated to play a crucial role for organ dysfunction. Since neuromuscular organ failure can be included into the spectrum of organ dysfunction that is observed during critical illness, the involvement of microcirculatory alterations in its pathogenesis seems obvious. Endothelial cell activation was observed in the vascular system of peripheral nerves. Specifically, immunoreactivity for E-selectin was observed during immunohistochemistry of peripheral nerves in critically ill patients. The endothelial activation leads to a damage within the blood–nerve barrier and increased microvascular permeability that is hypothesized to influence the endoneurial microenvironment. Changes within the fragile endoneurial microenvironment could be responsible for early fiber dysfunction and late fiber degeneration [45].

Hyperglycemia is a proven risk factor for critical illness polyneuropathy [46, 47]. Glucose uptake into nerves is mediated by the insulin-independent GLUT3 transporter. Due to the insulin independency and the high glucose affinity of the GLUT3 transporter are nerves subjected to severe hyperglycemia. Hyperglycemia leads to the production of ROS, which could be detrimental to nerves.

It was shown that hyperglycemia induces reactive oxygen species (ROS) production, and pathways associated with hyperglycemia mediated cell damage such as production of advanced glycation endproducts in endothelial cells [48]. Advanced glycation endproducts also play an important role in regulation of the blood–nerve barrier as they induce basement membrane hypertrophy, which disrupts the blood–nerve barrier [49]. A disruption of the blood–nerve barrier could as described above alter the nerval environment and lead to dysfunction and/or degeneration.

5.2.2.3 Channelopathy

Sodium and potassium are the main ions responsible for the transmission of action potentials along motor and sensory nerves. Alterations in potassium and sodium concentrations as well as modifications of participating channels could lead to a disrupted action potential transmission and a nerve dysfunction.

Abnormal membrane depolarization is commonly observed in critically ill patients. Patients with CIP present an inactivation of voltage-gated Na^+ channels, leading to reduced membrane excitability, which is a trigger for muscle weakness [50].

The knowledge regarding the pathophysiology of critical illness polyneuropathy is low due to a paucity of studies in humans. Therefore, most concepts are hypothetical, and further research is necessary to confirm or disconfirm the hypotheses.

Take Home Messages

Key pathophysiological concepts of critical illness polyneuropathy:

- Microcirculation insufficiency through endothelial cell activation causes peripheral nerve dysfunction through alterations in the endoneurial microenvironment
- Hyperglycemia induces ROS, which cause critical illness polyneuropathy through microvascular alterations leading to a blood–nerve barrier dysfunction
- Sodium channelopathy causes critical illness polyneuropathy through reduced membrane excitability

5

References

1. Osler SW. The principles and practice of medicine, designed for the use of practitioners and students of medicine. 1st ed. Edinburgh, London: Young J. Putland; 1892.
2. Latronico N, Fenzi F, Recupero D, Guarneri B, Tomelleri G, Tonin P, et al. Critical illness myopathy and neuropathy. Lancet. 1996;347(9015):1579–82.
3. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry. 1984;47(11):1223–31.
4. Koch S, Spuler S, Deja M, Bierbrauer J, Dimroth A, Behse F, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. J Neurol Neurosurg Psychiatry. 2011;82(3):287–93.
5. Shepherd S, Batra A, Lerner DP. Review of critical illness myopathy and neuropathy. Neurohospitalist. 2017;7(1):41–8.
6. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20.
7. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
8. Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, et al. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. 2014;40(4):528–38.
9. Bierbrauer J, Koch S, Olbricht C, Hamati J, Lodka D, Schneider J, et al. Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane. Crit Care Med. 2012;40(2):647–50.
10. Derde S, Hermans G, Derese I, Guiza F, Hedstrom Y, Wouters PJ, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med. 2012;40(1):79–89.
11. Klaude M, Mori M, Tjader I, Gustafsson T, Wernerman J, Rooyackers O. Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci (Lond). 2012;122(3):133–42.
12. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov. 2015;14(1):58–74.
13. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. N Engl J Med. 1996;335(25):1897–905.
14. Constantin D, McCullough J, Mahajan RP, Greenhaff PL. Novel events in the molecular regulation of muscle mass in critically ill patients. J Physiol. 2011;589(Pt 15):3883–95.
15. Hooijman PE, Beishuizen A, Witt CC, de Waard MC, Girbes AR, Spoelstra-de Man AM, et al. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. Am J Respir Crit Care Med. 2015;191(10):1126–38.
16. Tiao G, Hobler S, Wang JJ, Meyer TA, Luchette FA, Fischer JE, et al. Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. J Clin Invest. 1997;99(2):163–8.

17. Klaude M, Fredriksson K, Tjader I, Hammarqvist F, Ahlman B, Rooyackers O, et al. Proteasome proteolytic activity in skeletal muscle is increased in patients with sepsis. Clin Sci (Lond). 2007;112(9):499–506.
18. Helliwell TR, Wilkinson A, Griffiths RD, McClelland P, Palmer TE, Bone JM. Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. Neuropathol Appl Neurobiol. 1998;24(6):507–17.
19. Langhans C, Weber-Carstens S, Schmidt F, Hamati J, Kny M, Zhu X, et al. Inflammation-induced acute phase response in skeletal muscle and critical illness myopathy. PLoS One. 2014;9(3):e92048.
20. Cai D, Frantz JD, Tawa NE Jr, Melendez PA, Oh BC, Lidov HG, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell. 2004;119(2):285–98.
21. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Guiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011;96(4):E633–45.
22. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621–9.
23. Stibler H, Edstrom L, Ahlbeck K, Remahl S, Ansved T. Electrophoretic determination of the myosin/actin ratio in the diagnosis of critical illness myopathy. Intensive Care Med. 2003;29(9):1515–27.
24. Helliwell TR, Coakley JH, Wagenmakers AJ, Griffiths RD, Campbell IT, Green CJ, et al. Necrotizing myopathy in critically-ill patients. J Pathol. 1991;164(4):307–14.
25. Coakley JH, Nagendran K, Honavar M, Hinds CJ. Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. Intensive Care Med. 1993;19(6):323–8.
26. Sander HW, Golden M, Danon MJ. Quadriplegic areflexic ICU illness: selective thick filament loss and normal nerve histology. Muscle Nerve. 2002;26(4):499–505.
27. Gutmann L, Blumenthal D, Gutmann L, Schochet SS. Acute type II myofiber atrophy in critical illness. Neurology. 1996;46(3):819–21.
28. Ahlbeck K, Fredriksson K, Rooyackers O, Maback G, Remahl S, Ansved T, et al. Signs of critical illness polyneuropathy and myopathy can be seen early in the ICU course. Acta Anaesthesiol Scand. 2009;53(6):717–23.
29. De Letter MA, van Doorn PA, Savelkoul HF, Laman JD, Schmitz PI, Op de Coul AA, et al. Critical illness polyneuropathy and myopathy (CIPNM): evidence for local immune activation by cytokine-expression in the muscle tissue. J Neuroimmunol. 2000;106(1–2):206–13.
30. Khaleeli AA, Edwards RH, Gohil K, McPhail G, Rennie MJ, Round J, et al. Corticosteroid myopathy: a clinical and pathological study. Clin Endocrinol. 1983;18(2):155–66.
31. Danon MJ, Carpenter S. Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. Muscle Nerve. 1991;14(11):1131–9.
32. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288(22):2859–67.
33. Zochodne DW, Bolton CF, Wells GA, Gilbert JJ, Hahn AF, Brown JD, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain. 1987;110(Pt 4):819–41.
34. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.
35. Chen L, Nelson DR, Zhao Y, Cui Z, Johnston JA. Relationship between muscle mass and muscle strength, and the impact of comorbidities: a population-based, cross-sectional study of older adults in the United States. BMC Geriatr. 2013;13:74.
36. Fredriksson K, Hammarqvist F, Strigard K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab. 2006;291(5):E1044–50.
37. Jiroutkova K, Krajcova A, Ziak J, Fric M, Waldauf P, Dzupa V, et al. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. Crit Care. 2015;19:448.
38. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–23.
39. Carre JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010;182(6):745–51.
40. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, et al. Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. Am J Respir Crit Care Med. 2013;187(4):387–96.

41. Weber-Carstens S, Koch S, Spuler S, Spies CD, Bubser F, Wernecke KD, et al. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients. Crit Care Med. 2009;37(9):2632–7.
42. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology. 1996;46(3):731–6.
43. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev. 2015;95(3):1025–109.
44. Axer H, Grimm A, Pausch C, Teschner U, Zinke J, Eisenach S, et al. The impairment of small nerve fibers in severe sepsis and septic shock. Crit Care. 2016;20:64.
45. Fenzi F, Latronico N, Refatti N, Rizzuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. Acta Neuropathol. 2003;106(1):75–82.
46. Hermans G, Schrooten M, Van Damme P, Berends N, Bouckaert B, De Vooght W, et al. Benefits of intensive insulin therapy on neuromuscular complications in routine daily critical care practice: a retrospective study. Crit Care. 2009;13(1):R5.
47. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175(5):480–9.
48. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000;404(6779):787–90.
49. Shimizu F, Sano Y, Haruki H, Kanda T. Advanced glycation end-products induce basement membrane hypertrophy in endoneurial microvessels and disrupt the blood-nerve barrier by stimulating the release of TGF-beta and vascular endothelial growth factor (VEGF) by pericytes. Diabetologia. 2011;54(6):1517–26.
50. Koch S, Bierbrauer J, Haas K, Wolter S, Grosskreutz J, Luft FC, et al. Critical illness polyneuropathy in ICU patients is related to reduced motor nerve excitability caused by reduced sodium permeability. Intensive Care Med Exp. 2016;4(1):10.

Functional Outcomes Following Critical Illness

Abdulrahman A. Al-Fares and Margaret Herridge

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_6

Learning Objectives

- To understand the scope of medical complexity in survivors of critical illness
- To identify the evolution in and range of outcomes published over the past 40 years
- To identify if functional disabilities can co-occur, if they are affected by severity of illness or reasons for ICU admission, and if they are caused by ICU treatment or are an amplification of pre-existing disease before the ICU admission
- To understand why ICU and post-ICU rehabilitation interventions have failed to show benefit
- To appreciate the need for multidimensional outcome measures that deliver risk-stratified, focused, and tailored care.

Take-Home Message

Survivors of critical illness display a myriad of functional disabilities reflecting acquired medical complexity following discharge from ICU. Only a handful of interventions designed to improve disability have been effective, underscoring the limitation of applying generic interventions to a heterogeneous group of patients. Future outcome studies may wish to consider the simultaneous administration of multidimensional outcomes that – taken together – may help to inform patient- and family-oriented, risk-stratified, tailored, and focused care.

6.1 Background

Since the inception of modern intensive care units (ICU) following the polio epidemic in Copenhagen in the 1950s, there has been a steady evolution in care and outcomes [1]. Advancement of technology, therapeutics, and healthcare provisions in critical care have led to a growing population of survivors of critical illness and a resultant paradigm shift in delivery of care: from a focus on resuscitation and mechanical ventilation to the examination of interventions to reduce mortality and, more recently, morbidity. One of the important current challenges in critical care is the vast heterogeneity of our patient populations. The spectrum extends from the young patient with severe pulmonary hypertension awaiting heart-lung transplant supported on veno-arterial extracorporeal membrane oxygen (VA-ECMO) to the middle-aged woman with influenza-related acute respiratory distress syndrome (ARDS) to the elderly gentleman from a nursing home admitted with sepsis from a urinary tract infection. Prior health states and recovery after severe illness may be very different, and complex outcomes require nuanced and multidimensional measures to fully inform and optimize healthcare transitions and services required to optimize functional independence and quality of life.

In 1984, the renowned British theologist and medical ethicist Gordon Dunstan stated: "the success of intensive care is not, therefore, to be measured only by the statistics of survival as if each death is a medical failure, it is to be measured by the quality of life preserved or restored and by the quality of human relationships involved" [2]. In the decade following this, data on functional outcomes in ICU survivors began to emerge and showed that important physical and neuropsychological dysfunction extended beyond acute care hospitalization after critical illness. Most recently, this has been referred to as "post-intensive care syndrome" (PICS) [3] where acquired or exacerbated disability resulted in compromised long-term survival, frequent hospital or ICU readmissions, more specialist

services use, and higher costs [4]. Although compartmentalizing long-term outcomes into a syndromic phenomenon serves to elevate awareness about outcomes after critical illness and may help to simplify this construct for research purposes, it may not fully embrace the reality of the diverse and heterogeneous morbidities that may not benefit from the application of a simple, generic, and time-limited intervention. This may be an important factor in the failure of many targeted interventions applied during or after the ICU stay to improve quality-of-life outcomes [4–7].

In this chapter, we will review the scope and impact of post-ICU disability including its epidemiology, spectrum of functional outcomes, and associated risk factors. We will briefly review selected interventions for patients and caregivers and why these interventions have had limited success. We will conclude with a discussion about how the future of outcomes work may be re-shaped by embracing multidimensional outcome measures to achieve focused, risk-stratified, tailored follow-up care for survivors of critical illness and their families .

6.2 Scope of the Problem: Epidemiology of Functional Outcomes

Survivors of critical care acquire a complex recovery trajectory following their acute illness. In patients who are mechanically ventilated for more than 48 hours, 25–40% develop ICU-acquired weakness, and the reported prevalence is higher in patients with sepsis and prolonged ICU stay [8–11]. Moreover, physical weakness and inability to exercise are common with severe impairment reported in more than half of ARDS survivors [12, 13]. This muscle wasting and weakness attributed to polyneuropathy, myopathy, and disuse atrophy develops in 25% of patient requiring prolonged mechanical ventilation. Ventilator-induced diaphragmatic dysfunction is also common and occurs in half of patients with sepsis or following prolonged mechanical ventilation [14, 15].

The reported incidence of cognitive impairment after critical illness varies widely from 4% to 64% [16].The presence of delirium and its duration (only recognized in one-third of cases) are associated with neurocognitive dysfunction and mortality over the first year after critical illness [17, 18]. Up to one-third of ICU survivors report symptoms of depression, and almost one-tenth of patient have symptoms consistent with post-traumatic stress disorder (PTSD) [19]. Delusional memories and PTSD have been associated with altered health-related quality of life (HRQoL) in 70% of patients [20].

Over 50% of survivors of prolonged mechanical ventilation required assistance from family caregivers up to 1 year after their critical illness [21], and half of ARDS survivors were unable to return to work by 12 months following discharge from ICU [22, 23].

These figures highlight the burden of the acquired medical complexity following surviving critical illness and underscore the importance of understanding the extent of this disability and opportunities to mitigate it.

6.3 Traditional Long-Term Outcome Measures in Critical Care

The current focus on a continuum of care and long-term outcomes after critical illness originated from the longitudinal evaluation of ARDS patients. From small case series published shortly after the first description of ARDS by Ashbaugh and Petty in 1967 [24] to more detailed and thorough longitudinal studies of patients with ARDS, long-term

outcomes evolved from a focus on pulmonary function to generic quality-of-life measures, to encompass a comprehensive exploration of functional and neuropsychological outcomes. The focus thereafter expanded to include an evaluation of all survivors of critical illness and their caregivers and revealed numerous factors that result in this disability, medical complexity, and increased healthcare cost (Table 6.1).

6.3.1 Pulmonary Function Outcomes

Downs and colleagues were the first to report a case of a young woman with sepsis-related ARDS followed up for 5 months with pulmonary function tests [25]. Patients with ARDS were thought to be unique in representing a primary pulmonary lesion. Initial studies focused on pulmonary function testing as a surrogate for recovery and revealed variable obstructive and restrictive defects that improved within 6 months following extubation [26, 27]. Some investigators reported that the pulmonary dysfunction was unrelated to the initial lung injury but rather due to interventions applied in the ICU [26], while other investigators reported the contrary [27]. These observations were limited by small patient samples, incomplete follow-up, and heterogeneity of baseline pulmonary disease, leading to difficulty in understanding that the reported physical disability in ARDS survivors extended beyond pulmonary dysfunction.

6.3.2 Generic Health-Related Quality-of-Life (HRQoL) Outcomes

Outcome studies underwent a shift of focus from pulmonary function measures to the assessment patients' experience of major changes in their physical, emotional, and social well-being and captured as quality of life (QoL) of survivors [28–30]. Early studies used the generic Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36) [31], to determine the impact of ARDS on eight domains of physical and social functioning, role limitations due to emotional or physical problems, mental health, vitality, bodily pain, and general health perceptions. This scale is valid and quick to complete and allowed comparison with other patient populations.

Weinert and colleagues demonstrated that QoL profiles of ARDS survivors at 1 year after ICU discharge were significantly worse than the general population [28]. Schelling and colleagues reported good physical and social functioning with high rate of employment but impairment in psychosocial functioning [29]. Davidson and colleagues described significant reduction in generic and pulmonary disease-specific HRQoL most pronounced in the physical and social functioning domains, in survivors of trauma- or sepsis-related ARDS in comparison to matched patients without ARDS [30]. These studies were limited by cross-sectional or retrospective design, relatively low number of patients, potential of recall bias, and inability to assess baseline HRQoL. Moreover, decrements in physical function domains and subsequently exercise limitation were thought, at the time, to be related to residual pulmonary function abnormalities.

Several other tools were used to evaluate QoL. The Sickness Impact Profile (SIP) is a multidimensional health index consisting of 12 categories that can be grouped into physical dimension, psychosocial dimension, and other categories including sleep and rest, eating, work, home management, recreation, and pastimes. Tian and colleagues demonstrated that dysfunction in the physical dimension was most dominant, expect in younger patients

Table 6.1 Functional outcomes in ICU survivors

Study, year	Study type	Population	n.	Gender M/F	Age	Outcome measure	Timepoint of outcome assessment
Hopkins, 1999 [50]	Prospective longitudinal cohort	ARDS	55	25/30	45.5 (mean)	Neuropsychological test battery including intelligence, attention, concentration, memory, processing speed, and language	At hospital discharge and 1 year after onset of ARDS
Herridge, 2003 [12]	Prospective longitudinal cohort	ARDS	109	56/53	45 (median)	Clinical exam, PFT, 6MWT, SF-36	3, 6, and 12 months following discharge
Hopkins, 2005 [51]	Prospective longitudinal cohort	ARDS	120	33/41	46 (mean)	Comprehensive neuropsychological test battery including intelligence, attention, concentration, memory, processing speed, and language + SF-36	1- and 2-year follow-up after hospital discharge
Cheung, 2006 [40]	Prospective longitudinal cohort	ARDS	109	56/53	45 (median)	Clinical exam, PFT, 6MWT, SF-36, healthcare use, and cost data	3, 6, 12, 18, and 24 months following discharge
Iwashyna, 2010 [52]	Prospective cohort from large ongoing study	Sepsis	516	281/235	76.9 (mean)	ADL and IADL, mental state examination	Up to 4 surveys with follow-up mean of 8.3 years
Cuthbertson, 2010 [35]	Prospective longitudinal cohort	Mixed ICU except transplant	300	177/123	60.5 (median)	SF-36, EQ-5D	3, 6, and 12 months and 2.5 and 5 years after ICU admission
Herridge, 2011 [22]	Prospective longitudinal cohort	ARDS	109	56/53	45 (median)	Clinical exam, PFT, 6MWT, resting and exercise oximetry, CXR, SF-36	3, 6, and 12 months and 2, 3, 4, and 5 years following discharge

Mikkelsen, 2012 [56]	Cohort of multicenter RCT patients	ARDS	102	44/57	49 (median)	Battery of neuropsychological tests that assessed orientation, attention, working memory, short-term memory, reasoning, and executive function	2- and 12-month follow-up after hospital discharge
Needham, 2013 [43]	Prospective cohort ancillary to RCT patients	ARDS	525	NA	52 (mean)	SF-36, EQ-5D-3L, FACIT, MMSE, anxiety score, depression score, and PTSD score	6 and 12 months after ALI
Davydow, 2013 [124]	Prospective longitudinal cohort	Sepsis	471	223/248	75.3 (mean)	CES-D, ADL, IADL, cognitive status	Up to 4 surveys with follow-up mean of 7.1 years
Needham, 2013 [44]	Prospective cohort ancillary to RCT patients	ARDS	174	87/87	47 (mean)	Battery of neuropsychological tests that assessed executive function, language, memory, verbal reasoning and concept formation, attention, and working memory + arm anthropometrics, strength, PFT, 6MWT	6 and 12 months
Pandharipande, 2013 [18]	Prospective cohort	Respiratory failure or shock (cardiogenic or septic)	821	420/401	61 (median)	RBANS, Trails-B, CAM-ICU	Hospital admission, 3 and 12 months following discharge
Fan, 2014 [8]	Multisite prospective cohort	ARDS	224	123/111	49 (median)	Extremity, hand grip, MIP, anthropometrics, 6MWT, SF-36	3, 6, 12, and 24 months

(continued)

Table 6.1 (continued)

Study, year	Study type	Population	n.	Gender M/F	Age	Outcome measure	Timepoint of outcome assessment
Heyland, 2015 [87]	Multisite prospective cohort	Mixed medical and surgical ICU	610	338/272	84 (mean)	SF-36, frailty index	3, 6, 9, and 12 months after admission
Ferrante, 2015 [88]	Prospective cohort from large ongoing study	Mixed medical and surgical ICU and CCU	291	122/169	83.7 (mean)	Comprehensive home-based assessment including MMSE, CES-D, and physical frailty	Baseline and 18-month interval assessment
Needham, 2014 [41]	Prospective cohort	ARDS	203	100/103	48 (mean)	Manual muscle testing, 6MWD, SF-36 PF, arm muscle area, hand grip strength, MIP	6 and 12 months
Huang, 2016 [62]	Multicenter prospective cohort	ARDS	698	297/316	49 (mean)	HADS for anxiety and depression and IES-R for PTSD	6 and 12 months following ICU discharge
Herridge, 2016 [75]	Multicenter prospective cohort	Mixed medical and surgical ICU	391	226/165	59 (median)	FIM, 6MWT, upper and lower limb MRC, SF-36, IES, BDI-II	7 days and 3, 6, and 12 months from ICU discharge

ARDS adult respiratory distress syndrome, *PFT* pulmonary function test, *6MWT* six-minute walk test, *SF-36* Short-Form-36 Health Survey, *ADL* activities of daily living, *IADL* instrumental activity of daily living, *ICU* intensive care unit, *EQ-5D* health-related quality of life of 5 dimensions, *CXR* chest X-ray, *RCT* randomized controlled trial, *EQ-5D*-3L EQ-5D-three levels, *FACIT* functional assessment of chronic illness therapy, *MMSE* Mini-Mental State Exam, *PTSD* post-traumatic stress disorder, *CES-D* Center for Epidemiologic Studies Depression Scale, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *Trails-B* Trail Making Test, Part B, *CAM-ICU* Confusion Assessment Method for the ICU, *MIP* maximum inspiratory pressure, *SF-36 PF* SF-36 physical function, *HADS* Hospital Anxiety and Depression Scale, *IES-R* Impact of Events Scale-Revised, *FIM* Functional Independence Measure, *MRC* Medical Research Council, *Beck BDI-II* Depression Inventory-II

(30–50 years) where psychosocial dysfunction was more prominent, up to 6 months following discharge from ICU [32]. Subsequent to these reports, more investigators began examining QoL in survivors of critical illness up to 5 years after ICU discharge [33–36]. The most commonly used tools were SF-36 and EuroQoL-5D (EQ-5D). Overall critically ill patients had a lower quality of life than an age- and gender-matched population, with worst QoL seen in cases of severe ARDS, prolonged mechanical ventilation, severe trauma, and severe sepsis [36]. Although QoL tends to improve with time, some studies showed a decline between 2.5 and 5 years after the initial improvement to pre-morbid levels at 1 year [35].

6.3.3 Combining Functional Outcomes with HRQoL

McHugh and colleagues were the first to combine pulmonary function testing with SIP in ARDS survivors with 1-year follow-up after extubation [37]. There was considerable improvement within 3–6 months following extubation in pulmonary function and self-perceived health score that plateaued thereafter. Most importantly, total health score was significantly higher than the lung-related SIP indicating that patients typically did not attribute their health problems to breathing difficulties at least by 6 months following extubation. Nonetheless, etiology of this reported dysfunction was uncertain.

In a larger cohort of ARDS patients, Angus and colleagues combined pulmonary function tests with Quality of Well-Being (QWB) to assess HRQoL across two dimensions, function (physical activity, social activity, and mobility) and symptoms, which determine health utilities [38]. QoL was markedly impaired and resulted in a low quality-adjusted survival in the first year after ARDS. Furthermore, up to 70% of patients reported musculoskeletal symptoms at 12 months which the authors thought to be unrelated to ARDS.

The seminal longitudinal study by Herridge and colleagues evaluated ARDS patients at 3, 6, and 12 months with detailed in-person interview and complete physical examination, chest radiographs, pulmonary function testing, six-minute walk test, and QoL evaluation using SF-36 [12]. Survivors of ARDS manifested persistent functional limitation 1 year after being discharged from the ICU, which was largely due to muscle wasting, weakness, and fatigue, implicating extrapulmonary disease with impaired neuromuscular function as an important determinant of exercise limitation. This was corroborated by detailed radiological examination showing an absence of significant structural pulmonary changes that could explain the functional limitation [39]. This cohort continued to show persistent exercise limitation and lower than normal HRQoL at 2 years [40] and 5 years [22] after ICU discharge, with greater recovery in younger patients with most retaining the ability to live independently.

The detailed in-person evaluation by Herridge and colleagues revealed a myriad of physical impairments contributing to morbidity and medical complexity and included the following: entrapment neuropathy, heterotopic ossification and joint contractures, tracheal stenosis and vocal cord dysfunction, and cosmetic concerns related to scarring at tracheotomy, central line and chest tube sites, striae, and facial scars from prolonged noninvasive mask ventilation [12, 22]. The robust findings of prolonged exercise limitation and functional disability in ARDS survivors were confirmed by many other investigators [8, 41, 42]. Both Fan and Pfoh and colleagues examined specific muscle strength and outcomes by evaluating extremity, hand grip, and respiratory muscle strength using maximum inspiratory pressure (MIP), anthropometrics, and standardized manual muscle testing (MMT)

graded with the Medical Research Council (MRC) scale, which revealed objective muscle weakness in over one-third of patients at hospital discharge, that improved by 1 year but had persistence in physical dysfunction and HRQoL at 2 [8] and 5 years [42].

Needham and colleagues examined the relationship between protein and caloric intake in modulating muscle weakness of ARDS patients in a longitudinal ancillary study of the Early vs. Delayed Enteral Feeding (EDEN) trial of initial trophic versus full enteral feeding up to 6 days following randomization. Both patient-reported [43] and performance-based physical outcomes [44] showed below predicted values at 6 and 12 months with some improvement over time in both arms of the trial with no effect attributed to protein or caloric intake.

Although muscle wasting following critical illness occurred early and rapidly [45], the underlying mechanism of muscle weakness was postulated to be multifactorial and not fully understood. Corticosteroid-induced and critical illness-associated myopathy and polyneuropathy, and prolonged use of sedation and paralytic agents have been implicated as risk factors [12]. Duration of bed rest, immobilization, ICU length of stay, older age and pre-ICU comorbidities, and not severity of illness or ICU physiological derangement have been associated with acquired weakness and muscle dysfunction in patients with shock and ARDS [8, 13, 41, 42, 46]. The persistent muscle wasting and weakness generated interest in what has been described as intensive care unit-acquired weakness (ICU-AW) which is a consequence of a myosin depletion myopathy and axonopathy occurring in isolation or together [47]. Several molecular mechanisms of muscle and nerve injury have been studied including upregulation of the ubiquitin-proteasome pathway and marked proteolysis that begins within hours of critical illness [48]. While muscle repair after critical illness may be variable, recovery of contractile forces and muscle mass may be discordant at long-term follow-up [49].

6.3.4 Neuropsychological and Mental Health Outcomes

Early work in long-term outcomes after critical illness clearly indicated that cognitive dysfunction and mood disorders were important determinants of recovery.

6.3.4.1 Neuropsychological Outcomes

Hopkins and colleagues were the first to examine neuropsychological sequelae in ARDS survivors utilizing a battery of cognitive and psychological tests (Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale-Revised (WMS-R), Trail Making Test Parts A and B, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and the Faschingbauer Short Form Minnesota Multiphasic Personality Inventory (MMPI)) [50]. They were able to demonstrate cognitive and affective impairments in 100% of the cohort at hospital discharge. At 1-year follow-up, 78% of patients had all or at least one of impaired memory, attention, concentration, and/or decreased mental processing speed, with 30% exhibiting global cognitive decline. Even after follow-up for 2 years, similar findings were demonstrated by the same investigators with persistence of neurocognitive impairment in 47% of patients [51].

Iwashyna and colleagues were the first to explore cognitive impairment in survivors of severe sepsis, an older cohort of patients in comparison to ARDS survivors. They demonstrated moderate to severe cognitive impairment and decrements in function assessed by activities of daily living (ADLs) and instrumental ADLs (IADLs) [52]. The Bringing to Light the Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU)

study examined patients mechanically ventilated with respiratory failure or shock using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trail Making Test Part B and showed that at 3 months 40% of the patients had global cognitive scores that were similar to patients with moderate traumatic brain injury and 26% had scores that were similar to patients with mild Alzheimer's disease and persisted at 12 months in both older and younger patients [18]. A major limitation of most studies is the lack of information on baseline cognitive function, since patients with an abnormal cognitive baseline are at increased risk for critical illness [53].

Mechanisms of cognitive dysfunction are incompletely understood, but several factors are postulated. Severe sepsis is independently associated with a tripling in the odds of moderate to severe cognitive impairment [52]. In a mixed ICU population mechanically ventilated for sepsis and ARDS, increase in duration of delirium was an independent predictor of cognitive performance [18, 54]. Use of sedative and analgesic medication was not consistently associated with cognitive impairment [18]. Moreover, serial brain MRI studies have demonstrated global brain atrophy with preferential involvement of the superior frontal gyri, thalami, cerebellum, and hippocampal regions, all key areas for cognitive processing [55]. Older age, lower level of education, comorbid conditions, hypoxemia, duration of mechanical ventilation, fluid management, and dysglycemia are some of the other factors that may contribute to cognitive dysfunction [16, 50, 56]. Sleep disruption, a risk factor for delirium, remains an understudied potential contributor to cognitive impairment [57].

6.3.4.2 Mental Health Outcomes

Schelling and colleagues were the first to describe the occurrence of post-traumatic stress disorder (PTSD), using Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10), and associated decrements in the mental health domains on SF-36 in ARDS survivors [29]. Hopkins described moderate to severe depressive symptoms and anxiety which improved within the first year after ICU discharge but declined by 2 years [51]. Depressive symptoms were also observed in general medical ICU patients at 6 [58] and 9 months [59, 60]. Complex physical disability may contribute to social isolation and sexual dysfunction, and clinically important mood disorders may persist in over half of patients up to 5 years, which has been demonstrated across different cohorts [22, 61].

Risk factors for cognitive dysfunction are still incompletely understood, but candidates include hypoglycemia, ICU benzodiazepine use, morbid obesity, younger age, female sex, unemployment, alcohol misuse, and greater opioid used [62, 63].

6.3.5 Return to Work, Cost, and Pattern of Healthcare Utilization

Acquired complex disability after critical illness impacts the return to prior societal and familial roles and impacts patients, families, and society [64]. Return to work represents an important patient-centered outcome and meaningful metric of recovery after critical illness [65, 66]. Herridge and colleagues showed that 49% of ARDS survivors returned to work by 1 year [12], 65% by 2 years [40], and 77% by 5 years [22], mostly to their original employment. These findings have been replicated by others [23, 67].

Several studies examined risk factors associated with inability to return to work. In previously employed ARDS survivors enrolled in randomized controlled trials, older age, baseline comorbidities, longer duration of mechanical ventilation and hospital length of stay, and discharge to healthcare facility were associated with inability to return to work [23, 67]. In a

general ICU cohort ventilated for more than 24 hours and previously employed, major trauma, lower GCS, and increased hospital length of stay determined the inability to return to work at 6 months post-ICU admission and was related to worse functional recovery [68].

Detailed studies of cost after critical illness are still uncommon. In an ARDS cohort followed up for 2 years, Cheung and colleagues demonstrated that the largest proportion of healthcare costs was due to the initial hospital stay with 75% due to ICU costs [40]. Kamdar and colleagues found that 71% of ARDS survivors at 1 year reported earning losses averaging 43% of pre-ARDS annual income [23]. This effect persisted up to 5 years with loss of private health insurance and the need for government-funded insurance [67]. A propensity-matched study of sepsis survivors found similar findings [69]. Financial stress has been associated with female sex, having young children, and baseline financial disadvantage [70]. In patients receiving prolonged mechanical ventilation defined as 21 days or more, Unroe and colleagues estimated the cost for an independently functioning survivor at 1 year at a staggering $3.5 million US dollars [71].

6.4 Can Functional Disabilities Co-occur?

It is clear from outcomes work to date that researchers often examined one aspect of complex disability in isolation. One of the earlier instruments used in outcome research was the SF-36, which was thought to be a multidimensional outcome measure since it comprises both physical and mental components [12]. When the mental health (MH) domain and mental health component summary (MCS) of SF-36 was compared to other validated psychological instruments, it fared well in survivors of ARDS [72]. Nonetheless, MCS SF-36 cannot differentiate the constructs of depression and anxiety, and without the application of specific mental health instruments, important contributors to disability may be missed.

Marra and colleagues further explored this question using data from BRAIN-ICU [18] and Delirium and Dementia in Veterans Surviving ICU Care (MIND-ICU) [73]. In patients without baseline cognitive impairment or functional disability, the co-occurrence of newly acquired cognitive impairment, disability in ADLs, and depression existed among survivors of a critical illness and was present in 20% of patients at 1 year [74]. Education was found to be protective, and frailty was predictive of the development of long-term disability following critical illness. This led to the hypothesis that there are several subtypes to "PICS." In fact, this might indicate that long-term outcomes following critical illness transcend a syndromic construct and, rather, represent varying medical complexity that persists after ICU discharge.

6.5 Does Severity of Illness or Diagnosis at Admission Determine Functional Disability?

Admission to ICU is a potent marker of acquired multi-morbidities and medical complexity.

The RECOVER Program (Phase I) determined that severity of illness captured by the Acute Physiology and Chronic Health Evaluation (APACHE) II and Multiple Organ Dysfunction Syndrome (MODS) were not associated with outcomes in survivors of 7 days of mechanical ventilation [75]. This was confirmed recently by Griffith and colleagues in a general cohort of ICU survivors [46]. Furthermore, in patients who have been identified as persistently chronically ill, an entity that is thought to be distinct from PICS, admission diagnosis and physiological derangement, which predicted mortality on admission, pro-

gressively lost their predictive value in patients who spent 10 or more days in ICU [76]. Functional disability in ICU survivors may be determined by other factors, and not admission diagnosis, or severity of illness.

6.6 Is Functional Disability Caused by ICU or Is It an Amplification of Pre-existing Health Trajectory?

Age and pre-morbid health status are important contributors to long-term disability. Older age, frailty, and more comorbid illness are important modulators of outcome after critical illness [13, 77, 78]. This has recently been demonstrated in the RECOVER program, where age, ICU length of stay, and higher Charlson comorbidity score were strongly associated with 1-year mortality [75].

Average life expectancy has increased dramatically over the past century and is estimated to increase even further, but maximum longevity appears unchanged [79]. In ICU survivors of 1 week or more of mechanical ventilation, disability group stratification based on age (and ICU length of stay) conferred the worst 1-year recovery for older patients, which was found to be independent of admitting diagnosis and illness severity [75]. Moreover in patients 65 years and older, hospitalization with mechanical ventilation significantly increased 1-year mortality, and in survivors, disability and impairment of ADL were greater [80]. In trauma patients, age was found to be a significant risk factor for death [81]. Additionally, when patients 65 years and older with severe sepsis were examined for the effect of sepsis on the development of "geriatric conditions" (e.g., falls, incontinence, vision loss, hearing loss, and chronic pain), development of these conditions was not associated with severe sepsis but rather a reflection of pre-sepsis health trajectory [82]. Sepsis damages cellular and mitochondrial function and exhausts stem cells and contributes to physiological loss of reserve, organ decline, and reduced function [79].

Among octogenarians, even minimal impairment in pre-ICU cognitive status was associated with an increase in post-ICU disability over the 6 months after a critical illness; and moderate cognitive impairment doubled the likelihood of a new nursing home admission [83]. Elderly patients (>75 years) admitted to ICU rapidly lose autonomy as assessed by Barthel index and IADL reflecting lack of "physiological reserve" [84]. Within 1 year of surviving prolonged mechanical ventilation (>21 days), survivors experienced multiple transitions of care, and 67% required readmission to ICU [71]. Unroe and colleagues determined that older age and comorbid conditions were associated with poor outcomes. Furthermore, pre-existing comorbidity as determined by the Functional Comorbidity Index was recently found to be strongly associated with HRQoL and physical symptoms 1 year following critical illness [46], and two or more comorbidities are a strong risk factor for ICU mortality is a general medical and surgical ICU cohort [75]. These studies are limited by survivorship bias since follow-up functional data cannot be obtained on deceased participants between assessments.

Frailty is a multidimensional syndrome characterized by loss of physiologic and cognitive reserve that confers vulnerability to adverse outcomes [85]. Frailty is common in the ICU with approximately one-third of patients meeting frailty criteria [86]. Heyland and colleagues determined that lower frailty index, younger age, and fewer comorbidities were associated with physical recovery in octogenarians admitted to ICU for at least 24 hours at 1-year follow-up [87]. Ferrante and colleagues identified pre-ICU functional trajectories in octogenarians as an independent risk for worsening disability and 1-year mortality

[88]. Nevertheless, frailty in critical care is not only associated with older age [89]. Brummel and colleagues found that the Clinical Frailty Scale was independently associated with greater disability in IADLs and greater mortality at 3 and 12 months in patient 65 years and younger [86]. Moreover, Bagshaw and colleagues also confirmed that prehospital frailty was common and associated with higher rate of mortality at 1 year in a cohort with a mean age of 58 years [90].

6.7 Interventions to Aid Recovery from Acquired Critical Illness Disability

Exercise rehabilitation programs initiated after ICU discharge have reported inconsistent benefit [91]. Interventions targeting early ICU mobilization in previously functionally independent patients offer encouraging results [92], whereas other programs focused on nurse-led follow-up [5], disease management [93], physical therapist-led [7] and physical and nutrition-based rehabilitation [94, 95], or enhanced rehabilitation at home [96] have failed to show a clear benefit. Patient heterogeneity, generic interventions, and targeting muscle strength in isolation are some of the factors that account for this disparity [75, 97].

Despite the lack of rigorous neuropsychiatric rehabilitation studies [98], ICU diaries resulted in reduction in PTSD [99], and cognitive- and physical-based pilot studies confirmed feasibility and improvement in performance [100, 101]. Significant reduction of delirium reported by Schweickert and colleagues was attributed to physical rehabilitation rather than reduction in sedation [92]. Additionally, implementing the ABCDEF bundle reduced the risk of delirium [102]. For further details on rehabilitation intervention, please refer to ► Chaps. 19–24.

6.8 Integration of Patients' Caregivers

ICU survivor-caregiver dyad needs to be the new standard for care delivery and metric of choice in long-term follow-up and intervention studies following critical illness. Caregivers, family, or close friends identified compromised HRQoL, PTSD, emotional distress, depression, and anxiety associated with their role [103]. Moreover, 27% of caregivers of ARDS survivors followed up for 5 years reported anxiety, depression, or PTSD [22]. Caregivers who are challenged in their caregiving role may contribute to poor rehabilitation and worsened outcomes [104]. Chronic stress in caregivers promotes illness and has been identified as an independent risk factor for mortality [105]. Recently, Cameron and colleagues identified that caregivers' younger age, lack of social support, and lack of own life control were significantly associated with worse outcomes [106]. Further details could be found in ► Chaps. 17 and 18.

6.9 Need for Multidimensional Outcome Measures

Numerous instruments have been developed and used to assess ICU survivors over the past three decades or so. Recently, Turnbull and colleagues led a scoping review of cognitive, physical, and mental health outcomes in survivors of critical illness and found that in

the 425 studies published over the past 40 years, 250 different instruments (questionnaires, phone or personal interviews, physical examination, proxy interviews, chart reviews, and neurocognitive tests) were used to assess outcomes [107]. A meaningful synthesis of this literature is therefore difficult due to the vast heterogeneity in outcomes measured in each domain, the lack of standardization in the number and duration of follow-up, and the lack in combining performance-based and patient-reported or patient-important outcome measures. ICU survivors may experience positive emotions and life satisfaction not only functional disability that occurs after hospital discharge, therefore emphasizing the importance of patient-centered outcomes.

Amid this chaotic and incomplete picture (Fig. 6.1), it is prudent to utilize multidimensional outcome measures for long-term follow-up and intervention studies of critical illness survivors. In Table 6.2, we highlight some tools that may assess functional outcomes in this manner, globally and reliably. When selecting the most appropriate outcome measures, clinicians and researchers may wish to consider which outcome measures have robust clinimetric properties [108]. This includes the ability of an outcome measure to be valid, predictive, responsive, and applicable, with limited floor or ceiling effect. This is particularly important for a challenging environment such as ICU, where fluctuations in patient mental alertness, ability to follow commands, inability to mobilize, rapid changes in medical stability, and a confined space may impact on the choice, reliability, and validity of outcome measures.

The World Health Organization (WHO) International Classification of Functioning (ICF) framework provides a multidimensional conceptual model to guide patient assessment and evaluation [109]. Evaluation of long-term outcomes in the context of the ICF is an opportunity to reconcile disparate findings and consider new and unexplored interventions that may provide sustained improvement in the lives of survivors of critical illness

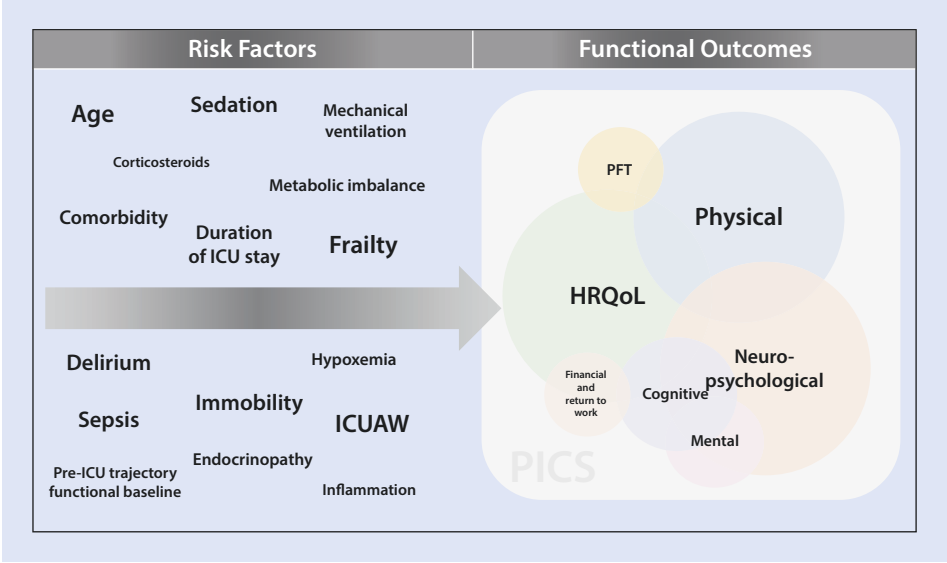


Fig. 6.1 Functional outcomes in survivors of critical illness reflecting the medical complexity of both risk factors and outcomes

Table 6.2 Candidate multidimensional outcome measures in physical, neuropsychological, and HRQoL domains

Outcome measure	Description and main features	Pros (+) and cons (–)
FIM [125]	Patient-centered measure of functional disability that captures the burden of care required by the patient daily, including progress during in-patient rehabilitation Two separate domains of items comprise motor domain of 13 items and cognitive domain of 5 items	(+) Predicts disability outcome and rehabilitation needs in diverse populations of patients (+) Reliable and valid
	Multidimensional measure which assesses self-care, sphincter control, transfers, locomotion, communication, and social cognition Total score between 18 and 126, ranging from complete dependence to complete independence, respectively	(–) Limitation to application in the ICU setting (e.g., stairs) and therefore inability to score (–) Ceiling effect in assessing change after discharge from rehabilitation
Barthel index [126]	Ordinal scale used to measure performance in ADLs Measure the capacity to perform 10 basic activities of daily living	(+) Highly reliable (+) Used widely and short without the need for experienced examiner
	Items divided into groups that relate to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and mobility (ambulation, transfers, and stair climbing) It gives a quantitative estimation of the patient's level of dependency with scoring from 0 (totally dependent) to 100 (totally independent)	(–) Psychological properties not evaluated well (–) Differential scoring if environment of the test changed (i.e., home vs outside)
Katz ADL index [127]	Developed for assessing functional status of elderly patients Assess the performance in 6 functions: bathing, dressing, toileting, transferring, continence, and feeding	(+) Easy and quick (+) Sensitive to change in health status
	Graded from dependent to independent with score from 2 to 6 Claimed to study prognosis and effectiveness of treatment and provide knowledge of the aging process Designed to be observer-completed	(–) Less correlative to scales examining mobility and house confinement (–) Limited in ability to measure small increments of change of rehabilitation
Lawton IADL [128]	Developed to assess more complex tasks such as financial and medication management, driving, shopping, house cleaning, and meal preparation	(+) Easy to administer (+) Valid and reliable
	IADL dependencies reflect higher-order functional impairments due to the cognitive demands required for successful task completion Score from 0 (dependent) to 8 (high function, independent)	(–) Variation in defining IADL dependency (–) Since its self-reported, might lead to over- or underestimation of ability

Table 6.2 (continued)

Outcome measure	Description and main features	Pros (+) and cons (–)
PFIT [129]	Developed for ICU patients who may not be able to mobilize away from bedside	(+) Reliable and responsive to change (+) Objective measure of endurance
	Contain 4 domains, (a) amount of assistance for sit to stand, (b) strength for shoulder flexion and knee extension, (c) marching in place, and (d) an upper extremity endurance task of arm elevation to 90° shoulder flexion Ability to assess vital sign response to exercise Each domain has a specific rating scale	(–) Limitation for not assessing ambulation, therefore likely to have floor and ceiling effect in ICU population (–) Not appropriate for patients who are unable to follow commands
FSS-ICU [130]	Ordinal scale similar to FIM and used for in-patient rehabilitation Consistent of 3 pre-ambulation categories, (a) rolling, (b) supine to sit transfers, and [3] unsupported sitting, and 2 ambulation categories: (a) sit to stand transfers and (b) ambulation	(+) Ideal for ICU settings (+) Valid and reliable
	Total score from 0 to 35. A score of 0 is assigned if a patient is unable to perform a task due to physical limitations or medical status	(–) Ceiling effect for long-term follow-up (–) Might take longer to complete depending on patient's functional status
HADS scale [131]	Developed to measure mood disorders of anxiety and depression in non-psychiatric patients, which is a self-assessment instrument Comprise 14 items, divided into 2 subscales, for depression and anxiety	(+) Correlates with psychiatric evaluation (+) Simple and easy to implement
	Avoids inclusion of items that could be present with physical illness, like loss of appetite and insomnia Patients assess their emotional state over the "past week"	(–) Does not include all diagnostic criteria for depression, therefore must inquire about appetite, sleep, and self-harm/suicidal thought if indicated
IES [132]	IES 15-item, disease-specific measure which assesses levels of subjective post-traumatic psychological distress. IES-R adds an additional 7 items for hyperarousal symptoms	(+) Simple and applicable (+) High sensitivity
	Provides specific measure of event intrusion and event-related avoidance, the two key elements of PTSD Scale of 0–5, related to thoughts during prior 7 days	(–) Low specificity (–) Does not correspond to DSM-based definition of PTSD

(continued)

Table 6.2 (continued)

Outcome measure	Description and main features	Pros (+) and cons (–)
Trail Making Test A and B [133]	Developed to assess attention, perceptual speed, cognitive flexibility, and visual memory	(+) Sensitive and quick to undertake (+) Valid and reliable and responsive
	Two-part instrument. Trial Making Test A is a test of simple visual motor attention that is scored in seconds. Trail Making Test B is a similar visual motor attention test that requires subjects to shift attention between two sets of stimuli and is measured in seconds An impaired score on the Trail Making Test B is indicative of cognitive impairment	(–) Affected by age and education (–) Significant ceiling effect in Trail Making Test A
TICS [134]	Global mental status test that can be administered either over the phone or face to face High correlation with MMSE	(+) High sensitivity and specificity (+) Can be used in individuals with severe visual and/or motor impairments
	Cognitive domains measured include orientation, concentration, short-term memory, language, praxis, and mathematical skills A modification, TICS-M [135], also includes delayed recall and verbal comprehension	(–) Limitation in hearing impairments (–) Repetition of words may affect concentration and recall
EQ5D-5L [136]	Generic instrument for describing and valuing health Based on 5 dimensions that describe health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	(+) Valid and reliable(+) Sensitive and responsive to change
	Each dimension is rated by 5 levels of severity It also includes an EQ VAS which respondents self-rate health on 20 cm vertical scale from worse to best healthcare imagined	(–) Might impose difficulty to respondents to deferential between "severe" and "extreme"
WHODAS 2.0 [137]	Based on the ICF concepts Comprises 6 domains: cognitive (understanding and communication), mobility (moving and getting around), self-care (hygiene, dressing eating, and staying alone), getting along (interacting with other people), life activities (domestic responsibilities, leisure, work, and school), and participation (joining in community activities)	(+) Reliable and valid (+) High sensitivity and specificity for measuring disability

Table 6.2 (continued)

Outcome measure	Description and main features	Pros (+) and cons (–)
	Available in 12- and 36-item versions Can be administered by interview, self, and proxy Rates disability by respondent subjective perspective Reflect on the previous 30 days	(–) Questions regarding employment status not integrated in subscale score (–) Some questions are complex and difficult to use in circumstances where the self-reported technique is problematic

FIM Functional Independence Measure, *ADL* activity of daily living, *IADL* instrumental activity of daily living, *PFIT* Physical Function ICU Test, *FSS-ICU* Functional Status Score for the ICU, *HADS* Hospital Anxiety and Depression Scale, *IES* Impact of Events Scale, *IES-R* IES-Revised, *TICS* telephone interview for cognitive screening, EQ *5D-5*L EuroQoL 5 dimensions 5-level, *EQ VAS* EQ visual analogue scale, *WHODAS* World Health Organization Disability Assessment Schedule 2.0, *ICF* International Classification of Functioning, Disability and Health Organization

[110]. Sequelae of acute illness are divided into three categories: damage to body structures, limitation in activities, and restriction in participation in social roles, with the addition by some scholars of QoL as a fourth category. These categories may be organized into a progression known as the disablement process, providing an approach to thinking about how tissue damage may lead to impaired QoL [111]. The ICF construct provides clarity in terms of organizing long-term outcome of ICU survivors into distinct phases such as alternation of baseline by an acute injury, causing tissue impairment, followed by functional limitations and disability in participation in social roles and subsequent effects on QoL. This framework may provide a useful scaffold to evaluate the challenges faced by ICU survivors and lend insight into optimal outcome measures to inform multidimensional disability.

For research purposes, it may be impractical to encompass all domains of ICU survivors acquired medical complexity. Moreover, for an outcome measure to be ideal, it must limit redundancy, be cost-effective, and entail limited burden to the patient while improving feasibility of conducting outcome assessments and research after hospital discharge. This led to the notion of examining core outcome set (COS) and applying core outcome measurement set (COMS) to future outcome research [112]. The proposed benefits of COS include a reduced potential for selective outcome reporting bias, enhanced data meta-analysis, and the inclusion of priority outcomes valued by stakeholders who were previously underrepresented in the research design process [113]. This was assessed by Needham and colleagues who identified eight core domains of outcomes including survival, physical function, mental health, pulmonary function, pain, muscle and/or nerve

function, cognition, and satisfaction with life or personal enjoyment (HRQoL). There was agreement on four of eight domains which could be completed quickly and simply via phone interview, thereby negating the need for in-person testing to minimize participant burden [114].

Nonetheless, the most comprehensive critical care research may seek to understand how illnesses and treatments interact to affect pathophysiology but also how patients and their families experience and make sense of illness and its aftermath [115]. The breadth and variability of morbidity after critical illness will elude us if we continue to study diseases or syndromes in isolation. Moreover, although COMS may specify the minimum assessment required without restriction of use of additional measurements, it may reduce opportunity to explore new domains or instruments due to limited resources and the risk of participant burden [113]. The spectrum of disability needs to be the focus of studies to determine robust themes and similarities across different disease states and gain an understanding of risk stratification and modification [116].

6.10 Risk-Stratified, Focused, and Tailored Follow-Up and Care

Risk-stratified, tailored, and responsive outcome measures that adapt to different baseline trajectories and evolving patient needs over time are desirable and necessary. Herridge and colleagues recently proposed the use of age and ICU length of stay to stratify survivors of 7 days of mechanical ventilation into four disability groups characterized by increasing risk for post-ICU functional disability and 1-year mortality based on the 7-day post-ICU discharge Functional Independence Measure (FIM) [75]. Precision medicine that stratifies patients based on disease subphenotype with distinct clinical characteristics and disparate outcomes may also offer insights into long-term outcomes. Seminal work by Calfee and colleagues identifying two district subphenotypes in ARDS patients by applying latent class analysis to major clinical trials clearly demonstrated hyperinflammatory subphenotypes that respond differentially to ventilatory and therapeutic management in ICU [117–119]. These findings support further pursuit of predictive enrichment strategies in critical care clinical trials and may be adjuncts in stratifying patients' long-term outcomes. Finally, stratification based on trajectory of recovery and dysfunction has been proposed by Iwashyna [120]. Stratifying patients into three groups of "The Big Hit," "The Slow Burn," and "Relapsing Recurrences" could be applied to critical care survivors and targeted clinical trials sought accordingly, with a trial of change in absolute level of function at maximal recovery, a trial seeking to change the trajectory of decline, or a trial seeking to maximize the number of impairment-free months, respectively.

The future of long-term outcome studies should build on past deficiencies and evolve to more focused and tailored care. Targeting person-centered care where what matters most to individuals during recovery is living independently, having a social role, being cognitively intact and pain-free, and resuming the ability to work [121]. Providing early intervention and support and clarifying expectations for transitions in care and recovery may decrease fears of the unknown for both caregivers and survivors. Ongoing family-centered follow-up programs may also help survivors regain independence and help caregivers manage their perceived responsibility for the patients' health [122]. Additionally, integrating geriatric principles into critical care to counteract vulnerability factors such as frailty, disability, and multi-morbidity is of utmost importance [123]. Critical illness survivors need care pathways that involve early post-ICU transfer to specialized in-patient programs that prioritize

comprehensive assessments of medical and/or surgical needs combined with tailored and graduated physical and neuropsychological rehabilitation and followed by long-term follow-up care [4]. Additionally, mandating education and formal transfer of care back to the primary care physician and closure of the care loop is invaluable.

Conclusions

There has been a steady rise over the recent decades in survivors of critical illness awed to the advancement of medicine and healthcare delivery. Although some patients make a dramatic recovery with no functional impairment, some survivors experience new and long-lasting physical, neuropsychological, mental disability with impairment in quality of life. A myriad of outcome measures has been examined over the past four decades but with somewhat limited meaningful synthesis drawn due to marked heterogeneity between patients and negligence of the diverse medical complexity, pre-morbid state, and frailty that can manifest in ICU survivors. This highlights the urgent need for patient-centered multidimensional outcome measures to be the focus of the future outcome research, to facilitate risk-stratified, tailored, and focused follow-up to be delivered.

References

1. Iwashyna TJ, Speelmon EC. Advancing a third revolution in critical care. Am J Respir Crit Care Med. 2016;194(7):782–3.
2. Dunstan GR. Hard questions in intensive care. A moralist answers questions put to him at a meeting of the Intensive Care Society, Autumn, 1984. Anaesthesia. 1985;40(5):479–82.
3. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9.
4. Herridge MS. Fifty years of research in ARDS. Long-term follow-up after acute respiratory distress syndrome. Insights for managing medical complexity after critical illness. Am J Respir Crit Care Med. 2017;196(11):1380–4.
5. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
6. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care. 2013;17(4):R156.
7. Elliott D, McKinley S, Alison J, Aitken LM, King M, Leslie GD, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. Crit Care. 2011;15(3):R142.
8. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42(4):849–59.
9. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. J Intensive Care Soc. 2015;16(2):126–36.
10. Tennila A, Salmi T, Pettila V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med. 2000;26(9):1360–3.
11. De Jonghe B, Cook D, Sharshar T, Lefaucheur JP, Carlet J, Outin H. Acquired neuromuscular disorders in critically ill patients: a systematic review. Groupe de Reflexion et d'Etude sur les Neuromyopathies En Reanimation. Intensive Care Med. 1998;24(12):1242–50.
12. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683–93.

13. Azoulay E, Vincent JL, Angus DC, Arabi YM, Brochard L, Brett SJ, et al. Recovery after critical illness: putting the puzzle together-a consensus of 29. Crit Care. 2017;21(1):296.
14. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013;188(2):213–9.
15. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42(5):853–61.
16. Sakusic A, Rabinstein AA. Cognitive outcomes after critical illness. Curr Opin Crit Care. 2018;24(5):410–4.
17. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276–80.
18. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
19. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med. 2014;2(5):369–79.
20. Burry L, Cook D, Herridge M, Devlin JW, Fergusson D, Meade M, et al. Recall of ICU stay in patients managed with a sedation protocol or a sedation protocol with daily interruption. Crit Care Med. 2015;43(10):2180–90.
21. Chelluri L, Im KA, Belle SH, Schulz R, Rotondi AJ, Donahoe MP, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. Crit Care Med. 2004;32(1):61–9.
22. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
23. Kamdar BB, Huang M, Dinglas VD, Colantuoni E, von Wachter TM, Hopkins RO, et al. Joblessness and lost earnings after acute respiratory distress syndrome in a 1-year national multicenter study. Am J Respir Crit Care Med. 2017;196(8):1012–20.
24. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
25. Downs JB, Olsen GN. Pulmonary function following adult respiratory distress syndrome. Chest. 1974;65(1):92–3.
26. Peters JI, Bell RC, Prihoda TJ, Harris G, Andrews C, Johanson WG. Clinical determinants of abnormalities in pulmonary functions in survivors of the adult respiratory distress syndrome. Am Rev Respir Dis. 1989;139(5):1163–8.
27. Klein JJ, van Haeringen JR, Sluiter HJ, Holloway R, Peset R. Pulmonary function after recovery from the adult respiratory distress syndrome. Chest. 1976;69(3):350–5.
28. Weinert CR, Gross CR, Kangas JR, Bury CL, Marinelli WA. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med. 1997;156(4 Pt 1):1120–8.
29. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med. 1998;26(4):651–9.
30. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA. 1999;281(4):354–60.
31. Chrispin PS, Scotton H, Rogers J, Lloyd D, Ridley SA. Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia. 1997;52(1):15–23.
32. Tian ZM, Miranda DR. Quality of life after intensive care with the sickness impact profile. Intensive Care Med. 1995;21(5):422–8.
33. Kvale R, Flaatten H. Changes in health-related quality of life from 6 months to 2 years after discharge from intensive care. Health Qual Life Outcomes. 2003;1(2):2.
34. Dowdy DW, Eid MP, Dennison CR, Mendez-Tellez PA, Herridge MS, Guallar E, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. Intensive Care Med. 2006;32(8):1115–24.
35. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010;14(1):R6.
36. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38(12):2386–400.
37. McHugh LG, Milberg JA, Whitcomb ME, Schoene RB, Maunder RJ, Hudson LD. Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med. 1994;150(1):90–4.

38. Angus DC, Musthafa AA, Clermont G, Griffin MF, Linde-Zwirble WT, Dremsizov TT, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163(6):1389–94.
39. Wilcox ME, Patsios D, Murphy G, Kudlow P, Paul N, Tansey CM, et al. Radiologic outcomes at 5 years after severe ARDS. Chest. 2013;143(4):920–6.
40. Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006;174(5):538–44.
41. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, et al. Risk factors for physical impairment after acute lung injury in a national, multicenter study. Am J Respir Crit Care Med. 2014;189(10):1214–24.
42. Pfoh ER, Wozniak AW, Colantuoni E, Dinglas VD, Mendez-Tellez PA, Shanholtz C, et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med. 2016;42(10):1557–66.
43. Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ. 2013;346:f1532.
44. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188(5):567–76.
45. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
46. Griffith DM, Salisbury LG, Lee RJ, Lone N, Merriweather JL, Walsh TS, et al. Determinants of health-related quality of life after ICU: importance of patient demographics, previous comorbidity, and severity of illness. Crit Care Med. 2018;46(4):594–601.
47. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35.
48. Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med. 2013;187(3):238–46.
49. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.
50. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LV. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(1):50–6.
51. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340–7.
52. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787–94.
53. Teeters DA, Moua T, Li G, Kashyap R, Biehl M, Kaur R, et al. Mild cognitive impairment and risk of critical illness. Crit Care Med. 2016;44(11):2045–51.
54. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513–20.
55. Gunther ML, Morandi A, Krauskopf E, Pandharipande P, Girard TD, Jackson JC, et al. The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study*. Crit Care Med. 2012;40(7):2022–32.
56. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12):1307–15.
57. Wilcox ME, Lim AS, McAndrews MP, Wennberg RA, Pinto RL, Black SE, et al. A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study. BMJ Open. 2017;7(7):e015600.
58. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31(4):1226–34.
59. Sukantarat K, Greer S, Brett S, Williamson R. Physical and psychological sequelae of critical illness. Br J Health Psychol. 2007;12.(Pt 1:65–74.

60. Sukantarat KT, Williamson RC, Brett SJ. Psychological assessment of ICU survivors: a comparison between the Hospital Anxiety and Depression scale and the Depression, Anxiety and Stress scale. Anaesthesia. 2007;62(3):239–43.
61. Bienvenu OJ, Friedman LA, Colantuoni E, Dinglas VD, Sepulveda KA, Mendez-Tellez P, et al. Psychiatric symptoms after acute respiratory distress syndrome: a 5-year longitudinal study. Intensive Care Med. 2018;44(1):38–47.
62. Huang M, Parker AM, Bienvenu OJ, Dinglas VD, Colantuoni E, Hopkins RO, et al. Psychiatric symptoms in acute respiratory distress syndrome survivors: a 1-year national multicenter study. Crit Care Med. 2016;44(5):954–65.
63. Dowdy DW, Dinglas V, Mendez-Tellez PA, Bienvenu OJ, Sevransky J, Dennison CR, et al. Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. Crit Care Med. 2008;36(10):2726–33.
64. Hodgson CL, Udy AA, Bailey M, Barrett J, Bellomo R, Bucknall T, et al. The impact of disability in survivors of critical illness. Intensive Care Med. 2017;43(7):992–1001.
65. Gabbe BJ, Simpson PM, Harrison JE, Lyons RA, Ameratunga S, Ponsford J, et al. Return to work and functional outcomes after major trauma: who recovers, when, and how well? Ann Surg. 2016;263(4):623–32.
66. Garland A. Labor market outcomes: expanding the list of patient-centered outcomes in critical care. Am J Respir Crit Care Med. 2017;196(8):946–7.
67. Kamdar BB, Sepulveda KA, Chong A, Lord RK, Dinglas VD, Mendez-Tellez PA, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. Thorax. 2018;73(2):125–33.
68. Hodgson CL, Haines KJ, Bailey M, Barrett J, Bellomo R, Bucknall T, et al. Predictors of return to work in survivors of critical illness. J Crit Care. 2018;48:21–5.
69. Thompson K, Taylor C, Jan S, Li Q, Hammond N, Myburgh J, et al. Health-related outcomes of critically ill patients with and without sepsis. Intensive Care Med. 2018;44(8):1249–57.
70. Khandelwal N, Hough CL, Downey L, Engelberg RA, Carson SS, White DB, et al. Prevalence, risk factors, and outcomes of financial stress in survivors of critical illness. Crit Care Med. 2018;46(6):e530–e9.
71. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med. 2010;153(3):167–75.
72. Pfoh ER, Chan KS, Dinglas VD, Cuthbertson BH, Elliott D, Porter R, et al. The SF-36 offers a strong measure of mental health symptoms in survivors of acute respiratory failure. A tri-national analysis. Ann Am Thorac Soc. 2016;13(8):1343–50.
73. Ely EW. MIND-ICU study: delirium and dementia in veterans surviving ICU care: Clinicaltrials.gov; 2018. Available from: https://clinicaltrials.gov/ct2/show/record/NCT00400062.
74. Marra A, Pandharipande PP, Girard TD, Patel MB, Hughes CG, Jackson JC, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. Crit Care Med. 2018;46(9):1393–401.
75. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med. 2016;194(7):831–44.
76. Iwashyna TJ, Hodgson CL, Pilcher D, Bailey M, van Lint A, Chavan S, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. Lancet Respir Med. 2016;4(7):566–73.
77. Haas B, Wunsch H. How does prior health status (age, comorbidities and frailty) determine critical illness and outcome? Curr Opin Crit Care. 2016;22(5):500–5.
78. Garland A, Olafson K, Ramsey CD, Yogendran M, Fransoo R. Distinct determinants of long-term and short-term survival in critical illness. Intensive Care Med. 2014;40(8):1097–105.
79. Aunan JR, Watson MM, Hagland HR, Soreide K. Molecular and biological hallmarks of ageing. Br J Surg. 2016;103(2):e29–46.
80. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. Am J Respir Crit Care Med. 2011;183(8):1037–42.
81. Goodmanson NW, Rosengart MR, Barnato AE, Sperry JL, Peitzman AB, Marshall GT. Defining geriatric trauma: when does age make a difference? Surgery. 2012;152(4):668–74; discussion 74-5.
82. Iwashyna TJ, Netzer G, Langa KM, Cigolle C. Spurious inferences about long-term outcomes: the case of severe sepsis and geriatric conditions. Am J Respir Crit Care Med. 2012;185(8):835–41.

83. Ferrante LE, Murphy TE, Gahbauer EA, Leo-Summers LS, Pisani MA, Gill TM. Pre-intensive care unit cognitive status, subsequent disability, and new nursing home admission among critically ill older adults. Ann Am Thorac Soc. 2018;15(5):622–9.
84. Somme D, Andrieux N, Guerot E, Lahjibi-Paulet H, Lazarovici C, Gisselbrecht M, et al. Loss of autonomy among elderly patients after a stay in a medical intensive care unit (ICU): a randomized study of the benefit of transfer to a geriatric ward. Arch Gerontol Geriatr. 2010;50(3):e36–40.
85. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):255–63.
86. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, et al. Frailty and subsequent disability and mortality among patients with critical illness. Am J Respir Crit Care Med. 2017;196(1):64–72.
87. Heyland DK, Garland A, Bagshaw SM, Cook D, Rockwood K, Stelfox HT, et al. Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. Intensive Care Med. 2015;41(11):1911–20.
88. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. JAMA Intern Med. 2015;175(4):523–9.
89. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ. 2014;186(2):E95–102.
90. Bagshaw M, Majumdar SR, Rolfson DB, Ibrahim Q, McDermid RC, Stelfox HT. A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care. 2016;20(1):175.
91. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev. 2015;(6):CD008632.
92. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
93. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. Am J Crit Care. 2007;16(5):447–57.
94. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med. 2016;193(10):1101–10.
95. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10.
96. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31(10):2456–61.
97. Hodgson CL, Iwashyna TJ, Schweickert WD. All that work and no gain: what should we do to restore physical function in our survivors? Am J Respir Crit Care Med. 2016;193(10):1071–2.
98. Hopkins RO, Suchyta MR, Farrer TJ, Needham D. Improving post-intensive care unit neuropsychiatric outcomes: understanding cognitive effects of physical activity. Am J Respir Crit Care Med. 2012;186(12):1220–8.
99. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42(5):1263–71.
100. Jackson JC, Ely EW, Morey MC, Anderson VM, Denne LB, Clune J, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. Crit Care Med. 2012;40(4):1088–97.
101. Brummel NE, Girard TD, Ely EW, Pandharipande PP, Morandi A, Hughes CG, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. Intensive Care Med. 2014;40(3):370–9.
102. Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. Crit Care Med. 2017;45(2):321–30.
103. Johnson P, Chaboyer W, Foster M, van der Vooren R. Caregivers of ICU patients discharged home: what burden do they face? Intensive Crit Care Nurs. 2001;17(4):219–27.

104. Evans RL, Bishop DS, Haselkorn JK. Factors predicting satisfactory home care after stroke. Arch Phys Med Rehabil. 1991;72(2):144–7.
105. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the caregiver health effects study. JAMA. 1999;282(23):2215–9.
106. Cameron JI, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. One-year outcomes in caregivers of critically ill patients. N Engl J Med. 2016;374(19):1831–41.
107. Turnbull AE, Rabiee A, Davis WE, Nasser MF, Venna VR, Lolitha R, et al. Outcome measurement in ICU survivorship research from 1970 to 2013: a scoping review of 425 publications. Crit Care Med. 2016;44(7):1267–77.
108. Hough CL. Improving physical function during and after critical care. Curr Opin Crit Care. 2013;19(5):488–95.
109. World Health Organization. International classification of functioning, disability and health. Geneva, Switzerland: World Health Organization; 2001.
110. Iwashyna TJ, Netzer G. The burdens of survivorship: an approach to thinking about long-term outcomes after critical illness. Semin Respir Crit Care Med. 2012;33(4):327–38.
111. Verbrugge LM, Jette AM. The disablement process. Soc Sci Med. 1994;38(1):1–14.
112. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. J Health Serv Res Policy. 2012;17(1):1–2.
113. Connolly B, Hough CL. Coloring by number? Core outcome measures and the canvas of intensive care unit survivorship. Am J Respir Crit Care Med. 2017;196(9):1087–9.
114. Needham DM, Sepulveda KA, Dinglas VD, Chessare CM, Friedman LA, Bingham CO 3rd, et al. Core outcome measures for clinical research in acute respiratory failure survivors. An international modified delphi consensus study. Am J Respir Crit Care Med. 2017;196(9):1122–30.
115. Gajic O, Ahmad SR, Wilson ME, Kaufman DA. Outcomes of critical illness: what is meaningful? Curr Opin Crit Care. 2018;24(5):394–400.
116. Whyte J, Barrett AM. Advancing the evidence base of rehabilitation treatments: a developmental approach. Arch Phys Med Rehabil. 2012;93(8. Suppl):S101–10.
117. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med. 2014;2(8):611–20.
118. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Respir Med. 2018;6(9):691–8.
119. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med. 2017;195(3):331–8.
120. Iwashyna TJ. Trajectories of recovery and dysfunction after acute illness, with implications for clinical trial design. Am J Respir Crit Care Med. 2012;186(4):302–4.
121. Ziegelstein RC. Personomics. JAMA Intern Med. 2015;175(6):888–9.
122. Czerwonka AI, Herridge MS, Chan L, Chu LM, Matte A, Cameron JI. Changing support needs of survivors of complex critical illness and their family caregivers across the care continuum: a qualitative pilot study of Towards RECOVER. J Crit Care. 2015;30(2):242–9.
123. Brummel NE, Ferrante LE. Integrating geriatric principles into critical care medicine: the time is now. Ann Am Thorac Soc. 2018;15(5):518–22.
124. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. Am J Geriatr Psychiatry. 2013;21(9):887–97.
125. Granger CV. The emerging science of functional assessment: our tool for outcomes analysis. Arch Phys Med Rehabil. 1998;79(3):235–40.
126. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61–5.
127. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.
128. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179–86.
129. Skinner EH, Berney S, Warrillow S, Denehy L. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. Crit Care Resusc. 2009;11(2):110–5.

130. Zanni JM, Korupolu R, Fan E, Pradhan P, Janjua K, Palmer JB, et al. Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project. J Crit Care. 2010;25(2):254–62.
131. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
132. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209–18.
133. Reitan R. Trail-making manual for administration, scoring and interpretation. Indianapolis: Indiana University Medical Center; 1958.
134. Brandt JSM, Folstein M. He telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol. 1988;1:111–7.
135. Welsh KABJ, Magruder- Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. Neuropsychiatry Neuropsychol Behav Neurol. 1993;6:103–10.
136. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
137. Ustun TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, et al. Developing the World Health Organization disability assessment schedule 2.0. Bull World Health Organ. 2010;88(11): 815–23.

Diaphragm Involvement

Boris Jung, Stefan Matecki, and Samir Jaber

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_7

Learning Objectives

- Main causes and pathophysiological keypoints of diaphragmatic dysfunction in the ICU
- To diagnose the diaphragmatic dysfunction
- To list the available countermeasures to limit the extent of diaphragmatic dysfunction

Take Home Messages

- Diaphragmatic dysfunction occurs rapidly and often in the critically ill
- It results from a myriad of phenomena and implicates both a rapid loss of force without loss of muscle mass and a delayed imbalance between an exaggerate proteolysis and an impaired protein synthesis generating further loss of muscle mass and force generation
- Maintaining spontaneous ventilation, avoiding neuromyotoxic drugs, and maintaining electrolytes and glucose control are the most usual ways to limit the generation of diaphragmatic dysfunction in the critically ill
- Temporary diaphragmatic pacing represents an interesting way of research

7.1 Introduction

Reduced mortality and the increasing prevalence of critical illness have resulted in a large and increasing numbers of survivors. However, survivors of critical illness can undergo profound changes in their lives as a result of their intensive care unit (ICU) stay. These changes, regrouped under the term postintensive care syndrome (PICS), are the consequences of physical [1], cognitive [2], and psychological [3] sequelae of the acute illness and the pre-ICU comorbidities. Among these changes, pulmonary function has been studied, mostly following acute respiratory distress syndrome (ARDS) [4, 5] as well as other organs and functions, but the literature about the impact of critical illness on specifically the respiratory muscles and the diaphragm is lacking.

The purpose of this review is to describe the impact of critical illness on the respiratory muscles' function in both the acute and the long-term periods as piece of the PICS puzzle.

7.2 Respiratory Muscles' Dysfunction in the ICU: Causes

Respiratory muscles' dysfunction in the ICU is multifactorial. In 1892, Osler already described a "rapid loss of flesh" in prolonged sepsis. Years after, Hussain et al. showed that ventilator failure in *Escherichia Coli* septic shock in dogs was the consequence of the fatigue of the respiratory muscles highlighting the strong deleterious impact of sepsis on respiratory muscles' contractility assessed by electromyogram [6]. The link between sepsis and respiratory muscles' dysfunction has been confirmed in multiple animal and human studies [7–9]. Mechanical ventilation (MV) by itself has been reported to be associated with diaphragm atrophy, and the first report was published in 1988 in 39 neonates or infants [10]. This condition was secondary named "Ventilator Induced Diaphragmatic Dysfunction" (VIDD) by Vassilakopoulos and Petrof [11]. Again, numerous animal studies have explored the cellular mechanisms linking controlled mechanical ventilation and

VIDD, and human studies confirmed the animal findings [7, 9, 12–15] using human diaphragmatic biopsies mostly in organ donors.

Eccentric contractions (contraction when the muscle lengthens) for instance when patients and ventilator are not synchronized may also generate diaphragm injuries, although the clinical evidence for this phenomenon is poor. Spontaneous breathing can also be associated with diaphragmatic dysfunction. Excessive loading or prolonged and intense resistive loading during acute respiratory failure may indeed be associated with self-inflicted respiratory muscles' injuries [6, 16].

Besides these two major causes (sepsis and mechanical ventilation) of respiratory muscles' dysfunction, several other acute cofactors contribute. Abdominal or thoracic surgery, neuromyotoxic drugs (myorelaxants, high dose of steroids, aminoglycosides, linezolid), hypophosphoremia, hypokalemia, prolonged hyperglycemia, malnutrition, and renal failure have been associated with respiratory muscles' dysfunction [9, 17–19].

7.3 Respiratory Muscles' Dysfunction in the ICU: Pathophysiology

Systemic and local muscular inflammation especially during sepsis, sympathetic nervous system activation [20], muscle inactivity [21], metabolic oversupply (diaphragm is exposed to excessive supply of energetic substrates relative to its metabolic needs which is very low when inactive) [15], and insulin resistance [22] are observed in the respiratory muscles during the acute phase of critical illness.

Consequently, several cellular pathways are activated or suppressed. Initial consequences involve contraction/relaxation homeostasis impairment and type 1 ryanodine receptor posttransductional oxidation and nitrosylation. Such modifications of the ryanodine receptor lead to calcium leak from the sarcoplasmic reticulum to the cytosol [20] activating calcium-dependent proteases. Mitochondrial dysfunction secondary to metabolic oversupply leading to reactive oxygen species release, mitochondria dynamics impairment, and further proteolysis activation has also been reported as an early phenomenon in VIDD [15]. Downstream of these early phenomena, not only excessive proteolysis (through the calpains, caspase 3, and the ubiquitin proteasome system) but also protein synthesis impairment (because of Insulin Growth Factor, AKT, and FOXO pathway inhibition) has been demonstrated [17, 18]. Autophagy, a self-degradative process important in response to nutrient stress and cell homeostasis impairment is then activated and is perceived as a physiologic response helping the cell for clearing damages organelles [23].

At the end of the road, all of these modifications lead to muscle atrophy, fibrosis, and loss of force.

7.4 Respiratory Muscles' Dysfunction in the ICU: Diagnosis

Although the purpose of the chapter is to describe the diaphragm involvement in the PICS, tools that can be used to diagnose inspiratory muscles' dysfunction may be useful to evaluate the diaphragm function after ICU discharge.

Inspiratory muscles' dysfunction can be diagnosed by performing pulmonary function tests sometimes at the bedside or more often in a pulmonary lab (e.g. sniff test) [24]. Surface electromyography has been suggested to evaluate diaphragm function although not being used in routine practice. Recently, ultrasonography of the diaphragm has been developed

and several measures can be performed. Thickness of the diaphragm, using a 10 MHz probe in the zone of apposition of the diaphragm to the rib cage, can be measured and is a surrogate of the diaphragm atrophy [25]. It decreases with the duration of mechanical ventilation [26], although reports suggest that it may increase [27] in some patients potentially because of muscle swelling and injury. Diaphragm excursion can be measured using a 3.5–5 MHz phased array probe. The probe is placed immediately below the right or left costal margin in the mid-clavicular line or in the right or left anterior axillary line and is directed medially and dorsally, so that the ultrasound beam reaches perpendicularly the posterior third of the corresponding hemi-diaphragm [25]. Diaphragm excursion has been suggested to be a surrogate of vital capacity but depends on the patient's motivation. Using the same window, thickening fraction can be evaluated as a surrogate of force production during quiet or forced breathing. Again, this measurement depends on the patient's motivation. No study has described the diaphragm recovery following critical illness using the ultrasound technique. The usual threshold values to define diaphragmatic atrophy are:

7

- End expiratory thickness below 2 mm or a drop of more than 20% compared to baseline thickness [26, 27]
- Diaphragmatic excursion during calm and spontaneous breathing lower than 10–15 mm [28]
- Diaphragmatic thickening fraction during calm and spontaneous breathing lower than 20–30% [29–31]

The gold-standard measurement in the intubated patient requires the use of bilateral anterior magnetic stimulation of the phrenic nerves and the measurement of transdiaphragmatic pressure using a double balloon (esophagus and gastric) probe [7, 13, 32]. This technique allows a measurement without the patient's participation, and a threshold of 11 cmH2O has been suggested to diagnose diaphragmatic dysfunction [7, 13, 33]. This technique in the non-intubated patient is much more difficult because of the necessity to avoid any leak (one should then use both a nasal clip and a mouth piece) during stimulation.

7.5 Respiratory Muscles' Dysfunction in the ICU: Management

Besides the causal treatment (e.g. sepsis), the intensivist can minimize the impact of the critical illness on the diaphragm function.

By promoting spontaneous breathing during MV, one can both limit the risk of metabolic oversupply and limit the risk of inactivity-associated atrophy [34]. Muscle contractile activity may also increase the diaphragm antioxidant capacity's release, limiting in theory the risk of the ryanodine receptor oxidation and the activation of the proteolysis cascade [35]. Eccentric contraction and excessive loading during spontaneous breathing should however be taken into account, and to date it is not completely sure whether maintaining spontaneous breathing in extreme situations such as acute respiratory distress syndrome is beneficial or deleterious for the diaphragm.

Inspiratory muscle training during the weaning period has been sparsely evaluated, and to date there is a lack of evidence to promote such initiative in the routine care (martin).

Although several drugs that inhibit the proteolysis cascade and/or promote the protein synthesis pathway have been tested in animal models, a few drugs have been evaluated in humans. To date, no drug has been approved to prevent or to treat diaphragmatic dysfunction in the critically ill. Theophylline and levosimendan [36] have demonstrated beneficial effects on diaphragm contractile activity, but these results are still preliminary.

Temporary diaphragmatic pacing has been recently evaluated as a method to limit the extent of diaphragmatic loss of force production. Diaphragmatic pacing can be achieved by direct implantation of electrodes in the diaphragm [37], by hooking the phrenic nerves during a surgical procedure [38, 39], or more recently by a transvenous (superior vena cava) stimulator [40, 41]. In animals, diaphragmatic pacing has been associated with the restoration of the proteolysis/protein synthesis balance [38] and less fiber atrophy [40] in a VIDD model. In humans, diaphragm electrodes can be surgically placed in the diaphragm [42, 43] during a laparoscopy or during a thoracic surgery [44]. Phrenic nerves can be hooked during cardiac surgery, and diaphragm pacing has been associated with an improvement in mitochondrial physiology and with less oxidative stress in the diaphragm [39, 45]. Diaphragmatic stimulation can also be achieved by transvenous stimulation using a central venous catheter [40]. Diaphragm capture was evaluated in 23 patients and could reduce the pressure time product from 10% to 48% without any serious adverse event [41].

7.6 Respiratory Muscles' Dysfunction in the ICU and PICS

Six- and 12-month limb muscle weakness and functional impairment have been described following critical illness [1, 46] as well as altered pulmonary function tests, persistent hypoxemia, and incapacity to exercise [5]. Despite strong evidence showing that respiratory muscles do also show persistent weakness and ultrastructural alterations months after ICU discharge, it is very likely that respiratory muscles' weakness plays a role in the PICS picture. The involvement of the diaphragm should be investigated specifically in the next few years.

References

1. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med. 2016;194(7):831–44.
2. Hopkins RO, Jackson JC. Short- and long-term cognitive outcomes in intensive care unit survivors. Clin Chest Med. 2009;30(1):143–53, ix
3. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340–7.
4. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
5. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683–93.
6. Hussain SN, Simkus G, Roussos C. Respiratory muscle fatigue: a cause of ventilatory failure in septic shock. J Appl Physiol Bethesda Md 1985. 1985;58(6):2033–40.
7. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013;188(2):213–9.

8. Demoule A, Molinari N, Jung B, Prodanovic H, Chanques G, Matecki S, et al. Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: a prospective longitudinal study. Ann Intensive Care. 2016;6(1):75.
9. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Crit Care Lond Engl. 2013;17(3):R120.
10. Knisely AS, Leal SM, Singer DB. Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. J Pediatr. 1988;113(6):1074–7.
11. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med. 2004;169(3):336–41.
12. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med. 2008;358(13):1327–35.
13. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet J-P, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med. 2011;183(3):364–71.
14. Hussain SNA, Mofarrahi M, Sigala I, Kim HC, Vassilakopoulos T, Maltais F, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. Am J Respir Crit Care Med. 2010;182(11):1377–86.
15. Picard M, Jung B, Liang F, Azuelos I, Hussain S, Goldberg P, et al. Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. Am J Respir Crit Care Med. 2012;186(11):1140–9.
16. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(9):1734–9.
17. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: ventilator-induced diaphragmatic dysfunction--human studies confirm animal model findings! Crit Care Lond Engl. 2011;15(2):206.
18. Petrof BJ, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. Curr Opin Crit Care. 2010;16(1):19–25.
19. Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43(10):1441–52.
20. Matecki S, Dridi H, Jung B, Saint N, Reiken SR, Scheuermann V, et al. Leaky ryanodine receptors contribute to diaphragmatic weakness during mechanical ventilation. Proc Natl Acad Sci U S A. 2016;113(32):9069–74.
21. Powers SK, Kavazis AN, Levine S. Prolonged mechanical ventilation alters diaphragmatic structure and function. Crit Care Med. 2009;37:S347–53.
22. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, et al. Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. Am J Respir Crit Care Med. 2013;187(4):387–96.
23. Azuelos I, Jung B, Picard M, Liang F, Li T, Lemaire C, et al. Relationship between autophagy and ventilator-induced diaphragmatic dysfunction. Anesthesiology. 2015;122(6):1349–61.
24. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518–624.
25. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med. 2013;39(5):801–10.
26. Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. Chest. 2012;142(6):1455–60.
27. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. Am J Respir Crit Care Med. 2015;192:1080–8.
28. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation*. Crit Care Med. 2011;39(12):2627–30.
29. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42(5):853–61.
30. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69(5):431–5.

31. Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in diaphragmatic thickness during the respiratory cycle predicts extubation success at various levels of pressure support ventilation. Lung. 2016;194(4):519–25.
32. Dres M, Dubé B-P, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med. 2017;195(1):57–66.
33. Dubé B-P, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A. Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. Thorax. 2017;72(9):811–8.
34. Jung B, Constantin J-M, Rossel N, Le Goff C, Sebbane M, Coisel Y, et al. Adaptive support ventilation prevents ventilator-induced diaphragmatic dysfunction in piglet: an in vivo and in vitro study. Anesthesiology. 2010;112(6):1435–43.
35. McClung JM, Kavazis AN, Whidden MA, DeRuisseau KC, Falk DJ, Criswell DS, et al. Antioxidant administration attenuates mechanical ventilation-induced rat diaphragm muscle atrophy independent of protein kinase B (PKB Akt) signalling. J Physiol. 2007;585(1):203–15.
36. Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HWH, van der Hoeven JG, et al. The calcium sensitizer levosimendan improves human diaphragm function. Am J Respir Crit Care Med. 2012;185(1):90–5.
37. Le Pimpec-Barthes F, Legras A, Arame A, Pricopi C, Boucherie J-C, Badia A, et al. Diaphragm pacing: the state of the art. J Thorac Dis. 2016;8(S4):S376–86.
38. Yang M, Wang H, Han G, Chen L, Huang L, Jiang J, et al. Phrenic nerve stimulation protects against mechanical ventilation-induced diaphragm dysfunction in rats. Muscle Nerve. 2013;48(6):958–62.
39. Martin AD, Joseph A-M, Beaver TM, Smith BK, Martin TD, Berg K, et al. Effect of intermittent phrenic nerve stimulation during cardiothoracic surgery on mitochondrial respiration in the human diaphragm⁎. Crit Care Med. 2014;42(2):e152–6.
40. Reynolds SC, Meyyappan R, Thakkar V, Tran BD, Nolette M-A, Sadarangani G, et al. Mitigation of ventilator-induced diaphragm atrophy by transvenous phrenic nerve stimulation. Am J Respir Crit Care Med [Internet]. 2016. Cited 22 Mar 2018; Available from: http://www.atsjournals.org/doi/10.1164/rccm.201502-0363OC.
41. Reynolds S, Ebner A, Meffen T, Thakkar V, Gani M, Taylor K, et al. Diaphragm activation in ventilated patients using a novel transvenous phrenic nerve pacing catheter. Crit Care Med. 2017;45(7):e691–4.
42. Onders RP, Markowitz A, Ho VP, Hardacre J, Novitsky Y, Towe C, et al. Completed FDA feasibility trial of surgically placed temporary diaphragm pacing electrodes: a promising option to prevent and treat respiratory failure. Am J Surg. 2018;215(3):518–21.
43. Onders RP, Elmo M, Kaplan C, Katirji B, Schilz R. Extended use of diaphragm pacing in patients with unilateral or bilateral diaphragm dysfunction: a new therapeutic option. Surgery. 2014;156(4):776–86.
44. Testelmans D, Nafteux P, Van Cromphaut S, Vrijsen B, Vos R, De Leyn P, et al. Feasibility of diaphragm pacing in patients after bilateral lung transplantation. Clin Transpl. 2017;31(12):e13134.
45. Mankowski RT, Ahmed S, Beaver T, Dirain M, Han C, Hess P, et al. Intraoperative hemidiaphragm electrical stimulation reduces oxidative stress and upregulates autophagy in surgery patients undergoing mechanical ventilation: exploratory study. J Transl Med [Internet]. 2016;14(1). Cited 22 Mar 2018. Available from: http://translational-medicine.biomedcentral.com/articles/10.1186/s12967-016-1060-0.
46. Dos Santos C, Hussain SNA, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.

Imaging

Peter J. M. Weijs, Wilhelmus G. P. M. Looijaard, Ingeborg M. Dekker, Robert Memelink, Sandra N. Stapel, Jeroen Molinger, and Heleen M. Oudemans-van Straaten

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_8

Learning Objectives

What you can expect in this chapter is to learn about methodologies that help you as a professional to get more insight into the body composition, nutritional status, and nutritional risk of post-intensive care patients. Different imaging methods can be used to assess and monitor loss, preservation, and gain of muscle mass. They are therefore tools that can be used for diagnosis and guiding treatment of (post-)intensive care patients. The choice for a certain method is usually made based on the method's availability, cost, expertise, and time consumption and not just on its accuracy. Results cannot be used interchangeably and require cooperation and expertise from different experts to be interpreted correctly. Also changes in fluid status confound measures of body composition during the acute phase of illness. Nevertheless, the use of imaging will become increasingly important due to the increasing interest in the many aspects of post-intensive care syndrome in which a poor nutritional status and a decrease in muscle mass play an important role.

8.1 Introduction

8

Imaging is the technique and process of creating visual representations of the interior of a body for clinical analysis and medical intervention. Imaging therefore is an important tool in the diagnostic process and may, e.g., be used to find out which tissue is traumatized or where a tumor is localized. This application of imaging may also provide information on the quality and function of organs or tissues. Imaging can also be used in a quantitative way, in order to assess body composition in terms of amounts of, e.g., muscle tissue and adipose tissue. Imaging is increasingly applied in clinical practice, and new developments improve application and use. Depending on the methodology, the assessment can be as specific as *intramuscular adipose tissue* and *appendicular skeletal muscle mass* or assess general health (BIA-derived phase angle). The goal of this body composition assessment, which can be part of a wider nutritional assessment, can be diagnostic, be used for risk assessment, as well as for monitoring. For instance, a smaller amount of total skeletal muscle mass may indicate a diminished nutritional reserve as well as a higher risk of poor outcome and could therefore be used to guide the nutritional treatment and rehabilitation of the patient.

In this chapter, we will focus primarily on the quantitative assessment of body composition by imaging using different methods, the advantages and limitations of these methods, and the specific clinical use in assessment and monitoring of the (post-)intensive care patient.

8.2 Methodology of Body Composition Imaging

Considering the basic aspects of body composition assessment, we generally make a distinction between direct methods, indirect methods, and double indirect methods. Direct methods are chemical analysis of body tissues and in vivo neutron activation analysis (IVNAA). They directly assess the amount of, e.g., chemical fat or nitrogen atoms, respectively. However, it should be clear that they cannot be used in clinical practice. Indirect methods are typically imaging methods like CT and DXA. In both these methods, a beam of radiation is applied to the tissue, and the tissue response (absorption, reflection) is visualized. These methods are validated against direct methods and less accurate than

direct methods; however, they are more applicable in clinical practice. The third level is the double indirect methods, like US and BIA. These methods use more assumptions that have to be met to accurately measure body composition; thus, the signals that result in images are less accurate compared to indirect methods as a quantitative assessment of body composition. On the other hand, these are usually measurements that are cheap, easy, and quick and therefore are often preferred in clinical practice.

In critically ill, the CT scan is often used as a diagnostic tool. Many patients therefore have a CT scan which is available at admission. The use of existing CT images for analysis of body composition is already applied in other patient populations, e.g., oncology patients. However, standard application of a CT scan for body composition analysis is not to be expected. Therefore, a variety of choices can be made in clinical practice. We will focus on the advantages and drawbacks of the different methods that are being used already. However, more methods should be expected in the near future.

In the following sections, we will provide some insight into the use of different imaging methodology for (post-)intensive care patients for current clinical practice.

8.3 Computer Tomography

Computed tomography (CT) scans can be used to provide clinicians with valuable and reliable information about body composition. However, since CT scans are expensive and expose patients to harmful radiation, the use of CT scans solely for body composition analysis or for follow-up is not feasible.

CT scanners use an X-ray generator with an opposite X-ray detector which rotates around a patient who is slowly being moved through the scanner to produce cross-sectional images (slices) of the scanned area. Hence, the name tomography came from the Greek words "tomos" meaning "slice" or "section" and "graphia" meaning "describing." As the X-rays pass through the body, they are attenuated (absorbed or scattered) by tissues before reaching the detector. Denser tissues such as bone attenuate X-rays more than less dense tissues, and this difference in attenuation is used to generate two-dimensional radiographs (comparable to conventional X-ray images). The many two-dimensional X-ray images that are generated from different angles are then digitally processed to produce cross-sectional images of the entire scanned area in different (axial, sagittal, and coronal) planes. The pixels in these images are assigned a value on the Hounsfield unit scale based on the attenuation of the tissues within the corresponding so-called voxel, which comprises the three-dimensional space of the pixel ∗ the CT slice thickness. On the Hounsfield unit scale, water has an attenuation of 0 Hounsfield units (HU), air is −1000 HU, and bone is typically above +1000 HU. All pixels in a cross-sectional CT scan image are gray, and based on their HU value they will be lighter (denser tissue) or darker (less dense tissue).

Body Composition Since the first CT scan in 1972, researchers have used CT scans to assess body composition to gain an insight into its relation with clinical outcome. Most research has been done in oncological patients, who have frequent CT scans as part of routine follow-up. In recent years however, this has expanded to other populations, among which are critically ill patients.

Although most radiology departments use software applications that can be used for body composition analysis, the most used research applications are SliceOmatic

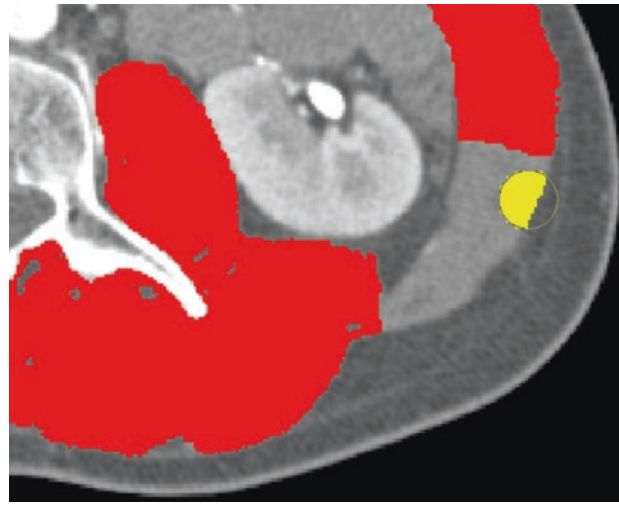


Fig. 8.1 Example of thresholding for muscle tissue. The bright yellow area within the yellow circle is identified as muscle tissue (HU between −29 and +150), while the darker (less dense) gray area within the circle is discarded. Red areas have already been identified as muscle tissues. Analyzed using SliceOmatic®

(TomoVision, Magog, QC, Canada) and open-source ImageJ (US National Institutes of Health, Bethesda, Maryland, USA). Agreement between the different applications is excellent [1]. The most basic method of analyzing a CT scan is by simply drawing a line around the tissue of interest (e.g., muscle or adipose tissue) and letting the software calculate the surface area within the outlined region. However, often more than one type of tissue is present within the outlined area (e.g., fat between muscle tissue, organs between visceral adipose tissue) which would be incorrectly identified as the tissue of interest. Therefore, it is advisable to use software capable of setting boundaries in HU (thresholding) which defines the density of tissues to be included in the analysis and excludes more and less dense tissues. Commonly used HU ranges are −29 to +150 for skeletal muscle, −190 to −30 for intermuscular and subcutaneous adipose tissue, and −50 to −150 for visceral adipose tissue [2] (Fig. 8.1).

Multiple sequential or single slice CT images can be analyzed to determine body composition. The easiest and fastest method is obviously single slice analysis, and in validation studies comparing the amount of muscle present on a single slice image to whole body muscle mass in cadavers, the amount of muscle present at the level of the third lumbar vertebra (L3) proved to be very well correlated to whole body muscle mass [2–4].

Software output includes both the surface area of the analyzed tissues in cm^2 and the mean density of the tissues expressed in HU. Muscle surface area can be normalized to height to produce the skeletal muscle index (SMI) expressed in cm^2/m^2. Mean skeletal muscle density can be used as a marker of muscle "quality" as opposed to "quantity," since a lower muscle density reflects more fatty infiltration of muscle or myosteatosis and could possibly also reflect muscle necrosis [5, 6].

In recent years, analysis of CT images has been automated, and special software modules are available to process large quantities of images in a short period of time [7]. However, adequate training and anatomical knowledge are still required to be able to correct automated analyses when necessary (Figs. 8.2 and 8.3).

CT Scan Analysis in Critical Care In the ICU, body composition assessed on CT scans made for clinical reasons at ICU admission has been used as a prognostic marker. Low muscle area at admission has been associated with higher in-hospital mortality, less ICU-free days and

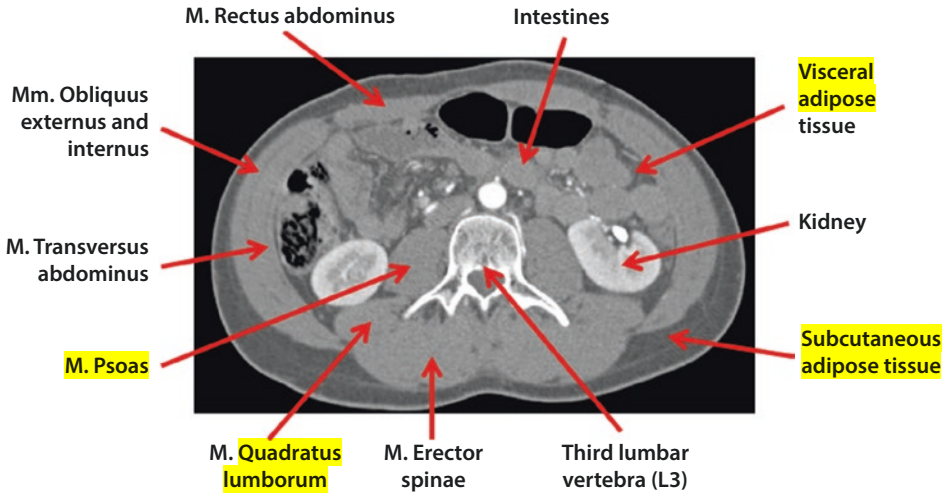


Fig. 8.2 The different muscles, visceral tissues, and organs present at the L3 level

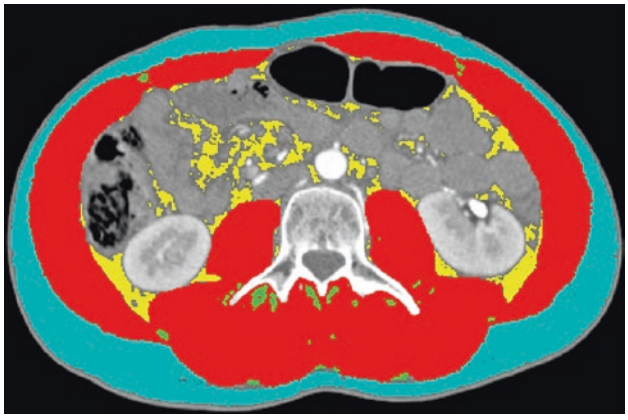


Fig. 8.3 Example of an analyzed L3 level CT slice. Red is muscle, green is intermuscular adipose tissue, yellow is visceral adipose tissue, and blue is subcutaneous adipose tissue. Analyzed using SliceOmatic®

less ventilator-free days, and a higher chance of being discharged to a nursing home [8, 9]. Additionally, low muscle quality (reflected by low skeletal muscle density) has been associated with a higher 6-month mortality and longer hospital stay, independent of the amount of muscle [10]. Muscle mass and quality on admission predicted mortality after adjustment for severity of disease and body mass index [9, 10].

Limitations Analysis of CT scans can provide clinicians with valuable and reliable information about body composition, especially about muscle quantity and quality which are important prognostic factors in ICU patients. However, several limitations and pitfalls need to be taken into account. Although the method of analyzing CT scans for body composition has been well-established, adequate training is required to accurately identify the correct tissues. Moreover, it should be noted that the scans were not originally made for the purpose of analyzing body composition and that the use of contrast agents, CT scanner tube voltage settings, and calibration can influence the results [11]. Patient factors can also influence reliability, as the position of the patient within the CT scanner can influence how muscles are

depicted. Furthermore, the presence of edema may confound the assessment of mass and quality and can sometimes make analysis very hard or even impossible.

Using CT scans for routine follow-up measurements is not feasible. The exposure to harmful ionizing radiation (about three times the yearly normal background radiation per abdominal CT scan), logistical difficulties and potential danger associated with the transport of critically ill patients, and costs are all factors which limit the usability of CT scan analysis to scans made during routine care. Furthermore, body composition is derived from regional images, e.g., the abdomen and thorax, and a relatively high or low appendicular muscle mass will not be assessed.

8.4 Ultrasound

A high percentage of survivors of critical illness are still functionally impaired after 12–18 months [12]; this is due to the rapid and early loss of skeletal muscle mass during intensive care stay [13–15]. Muscle function is related not only to muscle mass (quantity) but also to its quality (contractile versus non-contractile proportions), which in turn may be adversely affected as well. Measuring muscle mass is already a widely accepted tool within nutritional assessment in the ICU and also to assess muscle size. Qualifying lean tissue or muscle mass in clinical populations is of increasing importance due to the emerging associations between low muscle quality, low muscle mass/size, and poor aerobic capacity. Musculoskeletal ultrasound (MKUS) could not only be used to assess muscle mass through measuring thickness or cross-sectional area (CSA) but can also be used to see changes in morphology, histology, and muscle architecture. Here we will discuss all MKUS outcome parameters in regard to muscle quality and muscle size in terms of thickness, CSA, and volume.

Background US US is non-invasive and is carried out in vivo real time in a bedside setting. US scans display the "echogenicity" (brightness) of a muscle image which is based on the speed at which sound waves reflect back from different tissues within the muscle. Connective tissue is very dense, and the sound waves quickly reflect back to the transducer. Images of this tissue appear brighter (hyperechoic) on the scan. Water, on the other hand, allows the sound waves to pass through without resistance, and so they are not reflected back to the transducer. Images of scan areas containing water appear darker (hypoechoic): the higher the water content of the muscle, the darker the image will be [16].

US Imaging for Assessment of Muscle Mass Previous research found that gastrocnemius medialis and vastus lateralis muscle thickness are associated with functional performance in the older population, whereas quadriceps muscle thickness is associated with isometric and isokinetic knee extensor strength [17]. The use of MKUS to qualify muscle thickness or CSA is already emerging as a potential powerful clinical assessment tool in a ICU setting [18–20]. The advantage of measuring muscle size with the use of MKUS is the possibility to see changes within muscle groups versus the whole body lean mass. Histology and morphology are different within muscle groups, with direct consequences for the wasting patterns. A decrease of the rectus femoris CSA during the acute phase of critical illness is seen in a high percentage of the ICU population [19, 20]. The use of muscle CSA or thickness instead of only whole body lean mass will give insight into the muscle wasting patterns; which may guide early nutrition and/or early mobilization.

Assessment of Muscle Glycogen Glycogen depletion leads to marked muscle damage and an inability for muscle to recover and become anabolic. Low intramuscular glycogen is associated with an impairment of muscle ability to release Ca^{2+}, which is an important signal in the muscle activation. Depletion of intramuscular glycogen during prolonged critical illness may contribute to muscle fatigue and contractility by causing decreased Ca^{2+} release inside the muscle; which in turn will cause the inability to generate muscle force [21–24]. Thus, glycogen is conditional energy substrate for early mobilization. The metabolic demands of early mobilization are poorly understood in the ICU setting. There is significant heterogeneity in energy requirements between critically ill individuals undertaking the same functional activities [24]. Energy requirements are higher in the critically ill compared to healthy individuals; therefore, faster depletion of intramuscular glycogen could be expected [24–28]. Therefore, muscle glycogen assessment may provide essential information in the rehabilitation of the post-ICU patient [28].

Each gram of glycogen is tightly bound to 3 grams of water [29, 30]. When the muscle contains more glycogen, it also contains more water, producing a darker image. During critical illness, as glycogen is being metabolized, the bounded water leaves the muscle, which exposes the muscle fibers, which are denser than water. This enables the sound waves to be more easily reflected back producing a brighter image. Figure 8.4 shows, in predictable situations, the darker purple areas of the image can be assumed to contain more bounded water, hence more intramuscular glycogen. Regions with neon pinkish coloring correspond with low bounded water, which in turn represents low intramuscular glycogen content. Note: other energy-producing constituents of muscle such as protein, creatine, and carnitine are also tightly bound to water and may well contribute to the darkness of the image. The assessment of muscle glycogen levels by ultrasound was validated in two clinical studies [31, 32], conducted with trained cyclists during a 90-minute steady-state ride at moderate-high intensity and a 75-km time trial. The glycogen "score" generated by the MuscleSound® algorithm was compared to the gold standard of muscle biopsy.

Figure 8.5 shows the intramuscular glycogen (fuel) heat map of two subjects taken from the m. rectus femoris. Yellow is the fascia and aponeurosis; darker green/yellow

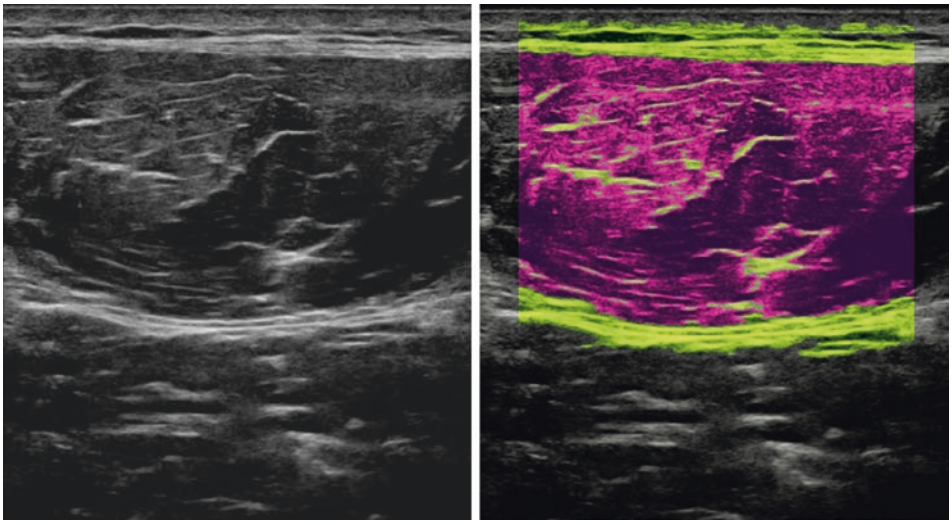


Fig. 8.4 MuscleSound® heat map glycogen rectus femoris short-axis and long-axis scan

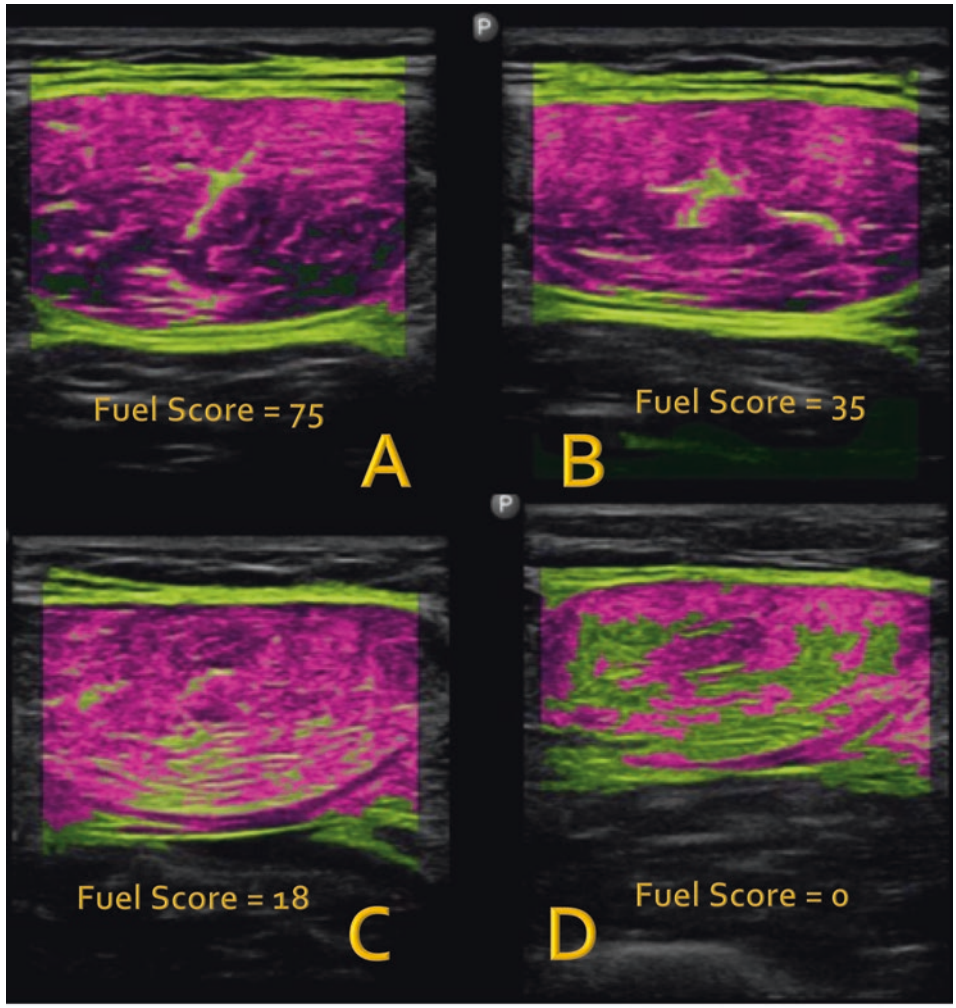


Fig. 8.5 MuscleSound® heat map glycogen rectus femoris short-axis scan

shows the higher echo intensities due to fat infiltration, fibrosis, and myonecrosis [15, 18, 20, 26, 33]. A and B are from an elite marathon runner age 28: pre- (**a**) and post- (**b**) marathon. (**c**, **d**) Is a young man age 25 with septic shock; C is taken on day 2 and D is taken on day 5 of ICU stay.

Skeletal Muscle Architecture (Fig. 8.6) Skeletal muscle architecture is an important muscle characteristic which plays a significant role in determining a muscle's force contribution to skeletal movement. It is defined by the pennation angle and the fascicle length. The pennation angle is the angle of insertion of muscle fascicles into the deep aponeurosis, and fascicle length is the length of the fascicular path between the superficial and deep aponeurosis [34]. The connective tissue sheath surrounding the fascicle is called the perimysium and is part of an efficient mechanism for transmission of contractile forces from adjacent

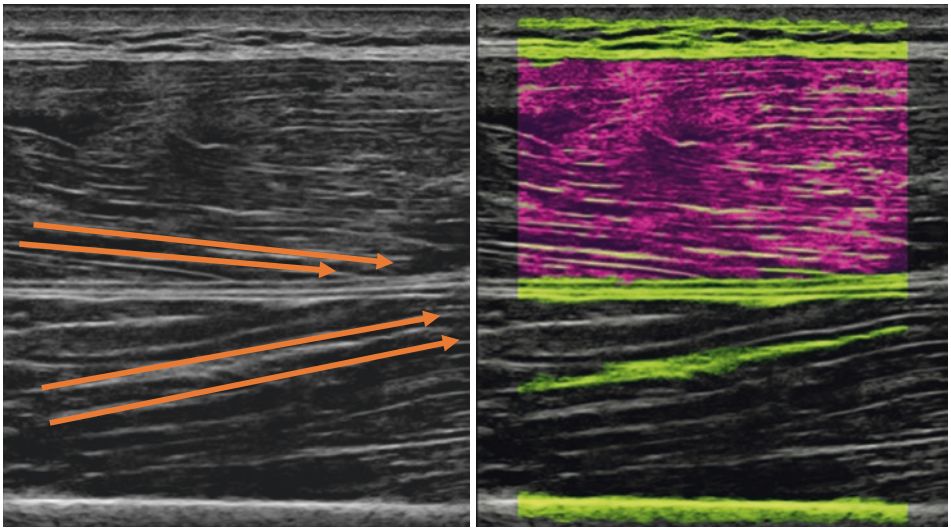


Fig. 8.6 Pennation angle rectus femoris long-axis scan, without and with MuscleSound® heat map

muscle fibers within fascicles [35, 36]. Pennation angle is essential for the transfer of forces from the muscle to the tendon. A pennation angle of 0° delivers 100% of contractility to the tendons, while a muscle with a pennation angle of 30° sends only 86% of its contractility to the tendons. Most human muscles range from 0° to 30° throughout the lower extremities [37, 38]. It is known that pennation angle can change during ICU stay due to fibrosis, myonecrosis [14, 18, 20, 26], and fluid accumulation in fascial planes, to which inflammation and infection may substantially contribute [18, 20, 26, 33]. Edema with cellar fasciitis dominates the early phase of critical illness, extending deeper within the muscle fascicles. This buildup of fluid within the muscle fascicles changes the morphology and architecture of the muscle; which gives rise to distinct changes of pennation angle of the fascicles. These changes of pennation angle are also seen after eccentric exercises with muscle damage [39], which results in an acute decline of muscle function. The physical function in an intensive care test score (PFIT-s) correlated very strongly with vastus lateralis pennation angle ($r = 0.81$, $p = 0.008$) [18].

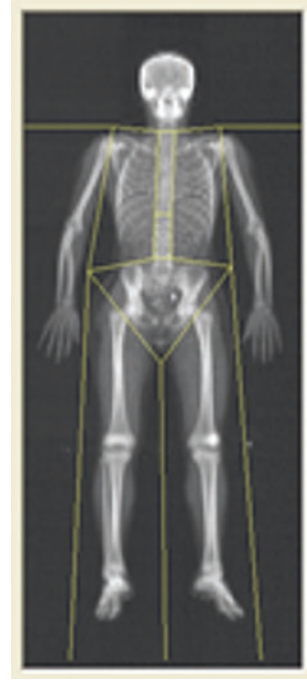
Dynamic Assessment Besides being non-invasive and available at the bedside, the other advantage is MKUS is the ability to dynamically scan the muscles in its function. Next to the normally used B-mode (brightness mode, showing a real-time image of the reflection of all US waves), there is also a M-mode (motion mode) option. M-mode ultrasound images display the changes in reflection of a single ultrasound wave over a period of time. It can therefore be used to visualize moving tissues, and M-mode MKUS imaging displays the motion of connective tissue within muscles. As muscle contraction is accompanied by motion of muscle tissue, M-mode MKUS can be used to assess the onset of deep muscle activity [40]. The intramuscular activation pattern can be connected to the motor unit recruitment strategy of force generation and fatigue resistance [41]. To assess recruitment patterns of muscle groups can help to tailor early mobilization and to evaluate intensive care-acquired muscle weakness (ICU-AW).

8.5 Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) is frequently used for assessment of bone mineral density and the diagnosis of osteoporosis [42]. It is also used to assess structural changes in the vertebrae and hip, induced by fractures or chronic wear with aging. However, DXA is increasingly used to assess whole body composition. It can not only differentiate between bone, lean tissue, and fat; it can also assess lean tissue in subregions. As in other patient populations, there currently is also an interest to assess appendicular skeletal muscle mass in this way for the post-intensive care patient [43].

The way DXA operates is by using a low-dose X-ray at two different levels of energy. The denser the tissue is, the more they will absorb the energy of the rays. When more energy is absorbed, less energy is detected by the sensor. By using all the information of the absorption of the different energy level X-rays at each pixel of the image, detailed imaging becomes available. Since bone is a very dense tissue, it lights up very clear, as shown in ◘ Fig. 8.7. Based on the detailed information, the bone tissue can be subtracted from the total at each pixel, and the remainder of the tissue is divided into fat tissue and lean tissue based on their radiation absorption. The accuracy of this latter assessment is somewhat less than for bone tissue.

As with any imaging technique, the positioning of the patient requires special attention. Especially when relatively small changes in lean tissue over time are the reason for the DXA assessment, standard operating procedures have to be followed accurately. Patients can be too long or too broad for the assessment table, although the software usually provides options to still perform an accurate body composition assessment. The software also provides the means for segmentation, so that arms and legs can be assessed



◘ **Fig. 8.7** Dual-energy X-ray absorptiometry image

separate from the trunk. By using skeletal landmarks, this segmentation procedure can reliably be performed at different time points for longitudinal assessment of the patient.

For the assessment of *fat mass,* the accumulated information provides the patient's body fat percentage. Moreover, it also provides the amount of fat present in limbs as well as in the abdomen. More specifically, using both landmarks and density, an assessment of visceral fat can be performed. This assessment is however less accurate than that of total fat mass.

Considering the interest in *muscle mass* loss, preservation, and gain of the post-intensive care patient, the DXA assessment of appendicular skeletal muscle mass has gained interest. It is essentially the bone-less and fat-less lean tissue in both arms and legs. Although some smaller quantities of other tissues are also included (e.g., skin, tendons, blood vessels, nerves), it is a good marker of muscle mass in the limbs (appendicular muscle mass). Since most muscle mass is in the limbs, appendicular muscle mass is also a good marker of the whole body muscle mass [44]. The assessment of upper leg muscle tissue by CT or MRI would be more accurate, however much less available (for the purpose of body composition), and also regionally limited.

8.6 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) is a fast, easy, and non-invasive method to estimate body composition.

Method During BIA measurement, an insensible alternating current is flowing through the body via skin electrodes, and the opposition (impedance) to the current flow is measured. Impedance (Z) consists of two components: resistance (R) and reactance (Xc). Reactance is the delay in conduction as a result of capacitance by cell membranes and tissue interfaces. Capacitance causes a phase shift or phase angle that is derived from R and Xc see (◘ Fig. 8.8). The impedance that the current flow encounters depends on body composition. Water- and electrolyte-rich components, such as blood and muscle mass, easily conduct the current, whereas fat mass and bone do not.

Equations and Assumptions Body composition can be estimated by equations combining BIA data with anthropomorphic data. In healthy individuals, these equations can be applied to estimate lean body mass (fat-free mass, body cell mass, muscle mass), fat mas, and volume compartments (intra- and extracellular water, total body water). However, the accuracy of the equations relies on several assumptions and prerequisites, such as a normal hydration status, a normal body geometry, and an accurate body length and weight. During critical illness, these assumptions and prerequisites are not met, and therefore BIA-derived equations are unreliable in the intensive care setting.

Use of Primary BIA Data Recent focus has shifted to the use of "raw" BIA data, R, Xc, and phase angle, which are independent of body weight and provide information about hydration, body cell mass, and cell membrane integrity. Phase angle is regarded as a marker of cellular health and has repeatedly been proven to be a predictor of morbidity and mortality in various patient groups, including the critically ill [45, 46].

BIA for Post-ICU Follow-Up Since BIA is a suitable method to estimate body composition when hydration status has returned to normal and the required assumptions can be met, it

may provide a simple and cheap biomarker to evaluate recovery of body health during revalidation and rehabilitation in post-ICU care clinics.

Figures 8.8, 8.9, and 8.10 show the principles of bioelectrical impedance analysis, phase shift, and phase angle.

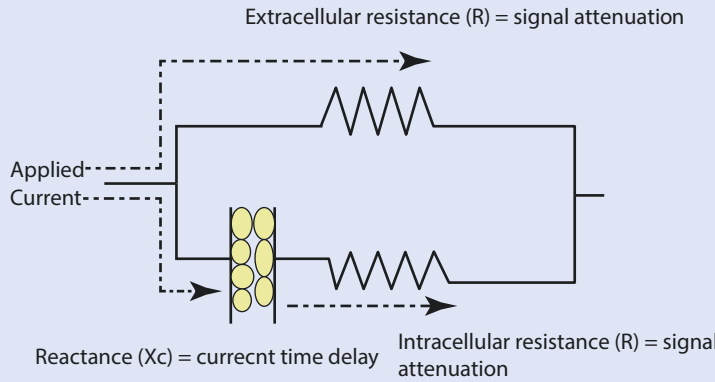


Fig. 8.8 BIA measures the opposition (impedance) to an applied current while passing through the extracellular and intracellular compartments. Impedance consists of two components: resistance (R), which reflects conductivity through ionic solutions, and reactance (Xc), the delay in the current flow, reflecting capacitance of cell membranes and tissue interfaces. (From Di Somma et al. [47])

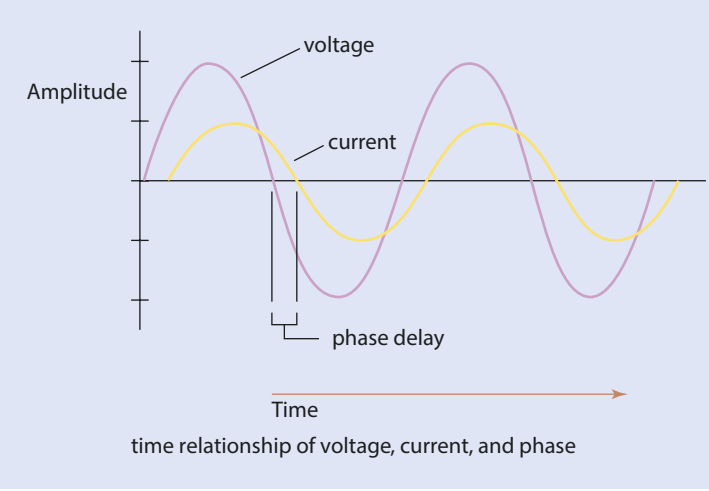


Fig. 8.9 Time relationship of voltage, current, and phase delay in the current flow measured by a phase shift (▶ https://www.biodyncorp.com/product/450/phase_angle_450.html)

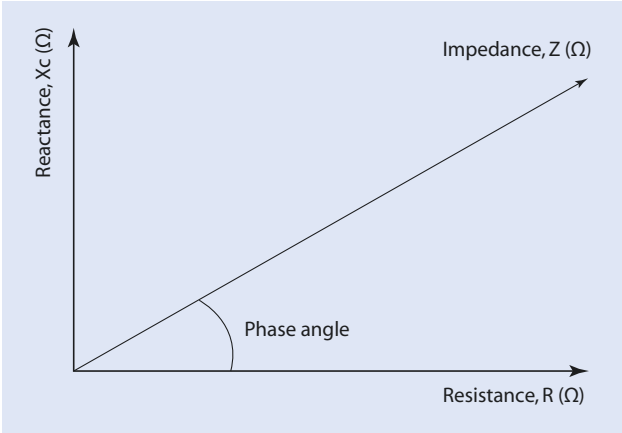


Fig. 8.10 The relationship between impedance resistance, reactance, and phase angle. Phase angle is quantified as arc tangent (Xc/R)∗180°/π

8.7 Practical Implications

Consider the use of imaging in every relevant clinical protocol.

8.8 Clinical Protocol

Apart from a focus on the acute disease, early identification of patients at risk of the detrimental consequences of loss of lean body mass and muscle wasting after ICU discharge has a priority as well. It is therefore important that physical reserves and nutritional status are assessed in each patient admitted to the ICU. In many hospitals nutritional screening is already standard procedure, but screening of physical reserves and fragility is not. Since the amount and quality of muscle mass may substantially modify the individual risk of dying, assessment of muscle mass seems important. Different imaging tools are available. CT scan, DXA, ultrasound, and BIA could be incorporated in this assessment in a protocolled way. Although each of these tools has their limitations, drawing attention to the importance of physical and nutritional reserves for ICU outcome is crucial. Monitoring will help to understand the consequences of diminished physical reserves on ICU admission, further loss during ICU stay, and recovery during rehabilitation. Monitoring is also crucial to develop and improve treatment. Physicians, physiotherapists, and dieticians should take their shared responsibility.

Conclusion

Intensivists, rehabilitation physicians, nurses, physiotherapists, and dietitians need to assess, know, understand, and monitor the physical condition and nutritional reserves of their patients during and after ICU admission. Several tools can be used to assess nutritional status, but the exceptional muscle loss that accompanies intensive care stay requires more specific imaging. CT scanning, ultrasound, and DXA are great tools to assess and

understand (changes in) muscle mass. CT scans and ultrasound also provide an insight into muscle quality. BIA offers a marker of general health. Imaging methods help us to measure loss, preservation, and gain of muscle. There are typical differences in accuracy, availability, costs, expertise, limitations, and time consumption between imaging methods. Choices have to be made according to the goals and within the limits of the hospital or care facility. Results from different methods cannot be used interchangeably in longitudinal assessments; therefore, cooperation between all experts practicing post-intensive care is required to provide accurate interpretation.

Take Home Messages

- Critically ill patients suffer from muscle wasting.
- Muscle wasting has severe short- and long-term consequences.
- Muscle mass can be assessed by CT scan analysis, ultrasound, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis (BIA).
- Low CT scan-derived muscle mass and quality on ICU admission as well as low BIA-derived phase angle predict higher mortality independent of BMI and severity of disease.
- Diagnostic CT scans are often available at ICU admission.
- Ultrasound and BIA analysis are available at the bedside.
- Ultrasound provides several promising tools to assess muscle quality and guide mobilization.
- All imaging tools have their limitations and critical illness-related fluid shifts confound their interpretation.
- Assessment of body composition may help to guide nutrition and mobilization during ICU stay and also during revalidation and rehabilitation after ICU discharge

8

Conflict of Interest PJMW has received funds from Baxter, Fresenius, Nestle, and Nutricia.

HMO has received research support from Fresenius, Nutricia, and Nestlé and speaker's and advisory honorary from Fresenius, Nestlé, Nutricia, Baxter/Gambro, and Abbott.

SS had received research support from Nestlé and Astellas.

JM has received speaker's and advisory honorary from MuscleSound, Nestlé, Nutricia, and Abbott.

References

1. van Vugt JL, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JW, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. J Cachexia Sarcopenia Muscle. 2017;8:285–97.
2. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85:115–22.
3. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97:2333–8.

4. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr. 1997;17:527–58.
5. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014;210:489–97.
6. Puthucheary ZA, Phadke R, Rawal J, McPhail MJ, Sidhu PS, Rowlerson A, et al. Qualitative ultrasound in acute critical illness muscle wasting. Crit Care Med. 2015;43:1603–11.
7. Popuri K, Cobzas D, Esfandiari N, Baracos V, Jagersand M. Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. IEEE Trans Med Imaging. 2016;35:512–20.
8. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17:R206.
9. Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014;18:R12.
10. Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Twisk JW, Oudemans-van Straaten HM, et al. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. Crit Care. 2016;20:386.
11. van der Werf A, Dekker IM, Meijerink MR, Wierdsma NJ. de van der Schueren MAE, Langius JAE. Skeletal muscle analyses: agreement between non-contrast and contrast CT scan measurements of skeletal muscle area and mean muscle attenuation. Clin Physiol Funct Imaging. 2018;38(3):366–72.
12. McNelly AS, Rawal J, Shrikrishna D, Hopkinson NS, Moxham J, Harridge SD, Hart N, Montgomery HE, Puthucheary ZA. An exploratory study of long-term outcome measures in critical illness survivors: construct validity of physical activity, frailty, and health-related quality of life measures. Crit Care Med. 2016;44(6):e362–9.
13. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683–93.
14. Puthucheary ZA, Phadke R, Rawal J, McPhail MJ, Sidhu PS, Rowlerson A, Moxham J, Harridge S, Hart N, Montgomery HE. Qualitative ultrasound in acute critical illness muscle wasting. Crit Care Med. 2015;43(8):1603–11.
15. Puthucheary Z, Montgomery H, Moxham J, Harridge S, Hart N. Structure to function: muscle failure in critically ill patients. J Physiol. 2010;588(23):4641–8.
16. Hill JC, Millan IS. Validation of musculoskeletal ultrasound to assess and quantify muscle glycogen content. A novel approach. Phys Sportsmed. 2014;42(3):45–52.
17. Selva Raj I, Bird SR, Shield AJ. Ultrasound measurements of skeletal muscle architecture are associated with strength and functional capacity in older adults. Ultrasound Med Biol. 2017;43(3):586–94.
18. Parry SM, El-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, Annoni R, Puthucheary Z, Gordon IR, Morris PE, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. J Crit Care. 2015;30(5):1151 e1159–14.
19. Mourtzakis M, Parry S, Connolly B, Puthucheary Z. Skeletal muscle ultrasound in critical care: a tool in need of translation. Ann Am Thorac Soc. 2017;14(10):1495–503.
20. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
21. Ørtenblad N, Westerblad H, Nielsen J. Muscle glycogen stores and fatigue. J Physiol. 2013;591(18):4405–13.
22. Knuiman P, Hopman MT, Mensink M. Glycogen availability and skeletal muscle adaptations with endurance and resistance exercise. Nutr Metab (Lond). 2015;12:59.
23. Ortenblad N, Nielsen J, Saltin B, Holmberg HC. Role of glycogen availability in sarcoplasmic reticulum Ca2+ kinetics in human skeletal muscle. J Physiol. 2011;589(Pt 3):711–25.
24. Black CSM, Grocott M. The oxygen cost of rehabilitation in mechanically ventilated patients. Am J Respir Crit Care Med. 2017;195:A2742.
25. Bear DE, Parry SM, Puthucheary ZA. Can the critically ill patient generate sufficient energy to facilitate exercise in the ICU? Curr Opin Clin Nutr Metab Care. 2018;21(2):110–5.
26. Molinger J, van der Hoven B, Gommers D. Non-invasive assessment of muscle histology during sepsis; a feasibility study in recognition of muscle wasting patterns. Poster presentation 17Th congress of European shock society. Paris; 13 Sept 2017.

27. Wischmeyer PE, Puthucheary Z, San Millan I, Butz D, Grocott MPW. Muscle mass and physical recovery in ICU: innovations for targeting of nutrition and exercise. Curr Opin Crit Care. 2017;23(4):269–78.
28. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care. 2015;19(Suppl 3):S6.
29. Olsson KE, Saltin B. Variation in total body water with muscle glycogen changes in man. Acta Physiol Scand. 1970;80(1):11–8.
30. Fernández-Elías V. Relationship between muscle water and glycogen recovery after prolonged exercise in the heat in humans. Eur J Appl Physiol. 2015;115:1919–26.
31. Nieman DC, Shanely RA, Zwetsloot KA, Meaney MP, Farris GE. Ultrasonic assessment of exercise-induced change in skeletal muscle glycogen content. BMC Sports Sci Med Rehabil. 2015;7:9.
32. Hill JC, Millan IS. Validation of musculoskeletal ultrasound to assess and quantify muscle glycogen content. A novel approach. Phys Sportsmed. 2014;42(3):45–52.
33. Puthucheary Z. An update on muscle wasting in ICU. Signa Vitae. 2017;13(Suppl 3):30–1.
34. Kuyumcu ME, Halil M, Kara Ö, Çuni B, Çağlayan G, Güven S, Yeşil Y, Arık G, Yavuz BB, Cankurtaran M, et al. Ultrasonographic evaluation of the calf muscle mass and architecture in elderly patients with and without sarcopenia. Arch Gerontol Geriatr. 2016;65:218–24.
35. Purslow PP. Muscle fascia and force transmission. J Bodyw Mov Ther. 2010;14(4):411–7.
36. Narici MV, Maganaris CN, Reeves ND, Capodaglio P. Effect of aging on human muscle architecture. J Appl Physiol (1985). 2003;95(6):2229–34.
37. Lieber RL, Friden J. Functional and clinical significance of skeletal muscle architecture. Muscle Nerve. 2000;23(11):1647–66.
38. Lieber RL, Friden J. Clinical significance of skeletal muscle architecture. Clin Orthop Relat Res. 2001;383(383):140–51.
39. Yu JY, Jeong JG, Lee BH. Evaluation of muscle damage using ultrasound imaging. J Phys Ther Sci. 2015;27(2):531–4.
40. Dieterich AV, Pickard CM, Deshon LE, Strauss GR, Gibson W, Davey P, McKay J. M-mode ultrasound used to detect the onset of deep muscle activity. J Electromyogr Kinesiol. 2015;25(2):224–31.
41. Lindberg F, Ohberg F, Brodin LA, Gronlund C. Assessment of intramuscular activation patterns using ultrasound M-mode strain. J Electromyogr Kinesiol. 2013;23(4):879–85.
42. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol Endocrinol Metab. 1996;271(6):E941–51.
43. Verreijen AM, Verlaan S, Engberink MF, Swinkels S, de Vogel-van den Bosch J, Weijs PJ. A high whey protein-, leucine-, and vitamin D-enriched supplement preserves muscle mass during intentional weight loss in obese older adults: a double-blind randomized controlled trial. Am J Clin Nutr. 2015;101(2):279–86.
44. Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler D, Gallagher D, Heymsfield SB. Skeletal muscle mass: evaluation of neutron activation and dual-energy X-ray absorptiometry methods. J Appl Physiol (1985). 1996;80(3):824–31.
45. Thibault R, Makhlouf AM, Mulliez A, Cristina Gonzalez M, Kekstas G, Kozjek NR, Preiser JC, Rozalen IC, Dadet S, Krznaric Z, Kupczyk K, Tamion F, Cano N, Pichard C, Investigators PAP. Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study phase angle project. Intensive Care Med. 2016;42(9):1445–53.
46. Stapel S, Looijaard W, Dekker I, Girbes ARJ, Weijs P, Oudemans-van Straaten HM. Bioelectrical impedance analysis derived phase angle at admission as a predictor of 90-day mortality in intensive care patients. Eur J Clin Nutr. 2018;72(7):1019–25.
47. Di Somma S, Lukaski HC, Codognotto M, Peacock WF, Fiorini F, Aspromonte N, Ronco C, Santarelli S, Lalle I, Autunno A, Piccoli A. Consensus paper on the use of BIVA in medicine for the management of body hydration. Emerg Care J. 2011;7(4):6–14.

Endocrinopathy of the Critically Ill

Nathalie Van Aerde, Lisa Van Dyck, Ilse Vanhorebeek, and Greet Van den Berghe

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_9

Learning Objectives

- At the end of this chapter, you should be able to:
- Describe the biphasic neuroendocrine alterations that mark critical illness.
- Understand some of the teleological explanations for neuroendocrine changes observed in the critically ill and current evidence for treatment strategies.
- Apprehend the plausible role of (long-term) neuroendocrine disturbances in the post-intensive care syndrome.

Take-Home Messages

- The neuroendocrine response to critical illness is biphasic. The (hyper)acute phase with hypercortisolism, hypersecretion of growth hormone uncoupled from insulin-like growth factor I, and suppressed thyroid and gonadal axes is generally considered adaptive, to provide endogenous substrates and postpone costly anabolism. The chronic phase is characterized by overall diminished hypothalamic output, leading to ineffective stimulation of the pituitary gland and an ongoing state of hypercatabolism, which is presumed to be detrimental.
- Observational data on the neuroendocrine (non)recovery after ICU stay are currently not available. Extrapolation from other fields, however, suggests that sustained neuroendocrine disturbances might be associated with long-term persistence of muscle weakness and cognitive dysfunction.
- Corticosteroid administration for (presumed) adrenal insufficiency in ICU should be limited to specific indications, given recent pathophysiological insights, lack of survival benefit, and scarcity of data concerning the long-term effects in prolonged critically ill patients. Administration of recombinant human growth hormone, thyroid hormone, or anabolic steroids to reactivate anabolic pathways in prolonged critical illness is currently not recommended. Administration of hypothalamic releasing factors appeared to be promising, but impact on clinical outcome remains to be investigated in adequately powered outcome studies.
- The endocrine aspects of critical illness need to be interpreted in the context of important polypharmacy on an ICU ward, with various potentially interfering drug-induced effects.

9.1 Introduction

Critical illness is the most severe form of physical stress a patient can endure. In response to threatened vital organ metabolism, marked neuroendocrine alterations occur, irrespective of the underlying condition for which a patient needed admission to the ICU [1, 2]. The neuroendocrine system attempts to maintain homeostasis through a highly conserved system of neuroendocrine axes with feedback loops, each of which comprises a central nervous system component, located in the hypothalamus and anterior pituitary, and a peripheral endocrine target organ hormone (Fig. 9.1).

The neuroendocrine response to critical illness shows a biphasic pattern with a distinct acute and prolonged phase. In the acute phase, the pituitary is actively secreting, but

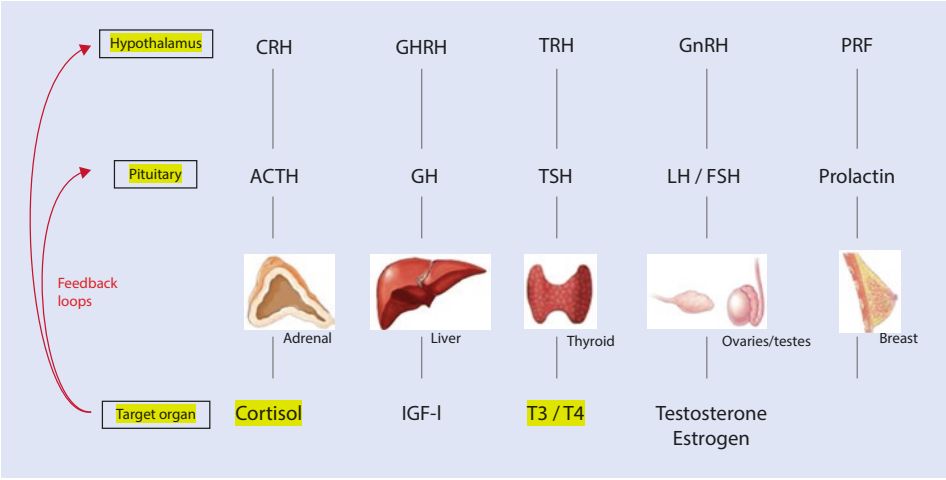


Fig. 9.1 Simplified overview of the neuroendocrine axes. Abbreviations: ACTH adrenocorticotropic hormone, CRH corticotropin-releasing hormone, FSH follicle-stimulating hormone, GH growth hormone, GHRH growth hormone-releasing hormone, GnRH gonadotropin-releasing hormone, IGF-I insulin-like growth factor-I, LH luteinizing hormone, PRF prolactin-releasing factor, TRH thyrotropin-releasing hormone, TSH thyroid-stimulating hormone (thyrotropin), T3 triiodothyronine, T4 tetraiodothyronine (thyroxine)

concentrations of all peripheral effector hormones apart from cortisol are low, partly due to target organ resistance [2]. When critical illness is prolonged, central output of all endocrine axes is diminished due to reduced hypothalamic function, which predominantly explains suppression of peripheral hormones in this phase [2]. Various drug-induced effects can further influence these alterations and make their interpretation complex on a patient level, especially in light of common polypharmacy in ICU wards (Table 9.1). The acute phase of the neuroendocrine stress response is generally considered adaptive as it provides substrates to maintain vital organ metabolism, while a persistently activated stress response and its associated alterations in effector hormone concentrations are suspected to contribute to the development of muscle weakness, increased susceptibility to infections, cognitive dysfunction, and high risk of death seen in prolonged critically ill patients [3–6]. Although it has been shown that the pituitary can be reactivated in prolonged critical illness by administration of central secretagogues, clinical usefulness of this intervention has only been partially investigated [7–9]. Further investigation is warranted, given evidence in other medical fields indicating that chronic hypercortisolism and a chronic lack of growth hormone, thyroid hormone, and testosterone are associated with loss of lean body mass, weakness, and cognitive dysfunction [10–13]. Importantly, these are the main morbidities seen in ICU survivors, collectively referred to as the post-intensive care syndrome or legacy of critical illness [4–6, 14, 15]. Hence, this may suggest that the neuroendocrine disturbances of critical illness, or non-recovery of the disturbances after resolution of the critical illness, could contribute to the post-intensive care syndrome.

In the following sections, we provide an overview of the neuroendocrine changes that occur during critical illness, their potential causes and consequences, plausible interventions, and their implications for daily care, with attention for a potential role in the post-intensive care syndrome.

Table 9.1 Medications with influence on the neuroendocrine axes

	Working site, action	Effect	Reference
ICU			
Vasoactive agents			[109–111]
Dopamine	Central, inhibitory	↓Prolactin ↓TSH → ↓T4 ↓GH ↓LH → ↓Testosterone	
Sedatives			[111–114]
Etomidate	Peripheral, inhibitory	↓Cortisol (via 11β-hydroxylase)	
Opioids	Central, combined	↓Cortisol, ↑ prolactin, ↑GH	
Benzodiazepines	Central, inhibitory	↓Cortisol	
Barbiturates	Peripheral, inhibitory	↓ T4 (↑metabolization)	
Antifungals: azoles:			[114]
Ketoconazole	Peripheral, inhibitory	↓Cortisol (via 17α-hydroxylase), ↓Testosterone (via 17,20-lyase, via 17α-hydroxylase)	
Miconazole	Peripheral, inhibitory	↓Cortisol (via 21-hydroxylase)	
GI-acting therapies			[111, 115]
Metoclopramide Somatostatin	Peripheral, inhibitory Central, inhibitory	↓Aldosterone ↓TSH ↓GH ↓PRL ↓LH	
Iodine (iodine-based disinfectants, contrast, amiodarone)(acute)	Peripheral, variable	↓T4 (↓release: Wolff-Chaikoff) ↑T4 (pre-existing goiter, thyroiditis) ↓T3 (↓deiodination: amiodarone)	[95, 111]
Cardiac drugs			[111]
Beta-adrenergic blockers	Peripheral, inhibitory	↓T3 (↓deiodination)	
Furosemide	Peripheral, inhibitory	↓T4 (↓protein binding →↑metabolization)	
Exogenous steroids			[111, 116, 117]
Corticosteroids	Central, inhibitory	↓CRH → ↓ ACTH → ↓ Cortisol ↓TSH → ↓T4 ↓GnRH +↓LH (species specific)	
	Peripheral, inhibitory	↓T3 (↓deiodination)	

Table 9.1 (continued)

	Working site, action	Effect	Reference
Pre-ICU			
Exogenous steroids Oral contraceptives Anabolic steroids Medroxyprogesterone Megestrol acetate Corticosteroids	Central and peripheral, inhibitory	↓CRH → ↓ ACTH → ↓ Cortisol ↓TBG → ↓ T4 (↑metabolization) ↓TBG (estrogen)	[111, 118, 119]
Opioids (prolonged)	Central, inhibitory	↓ GnRH → ↓ LH, FSH ↓ ACTH → ↓ Cortisol, DHEAS	[120]
Psychotropic drugs			[111]
Lithium	Peripheral, inhibitory	↓T4 (↓T4 release)	
Anti-epileptic drugs	Peripheral, inhibitory	↓T4 (↑hepatic metabolization)	
Bexarotene, retinoid X receptors (RXR) ligand	Central, inhibitory	↓TSH → ↓T4	[103, 121]

Abbreviations: *GI* gastro-intestinal, ↓ reduced concentration (due to reduced secretion – or if other mechanism depicted between brackets), via inhibition

9.2 Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis contributes to the regulation of immune function, reproduction, growth and metabolism, and their adaptation during stress [1, 16]. Under physiological conditions, cortisol secretion from the adrenal cortex occurs in episodic bursts due to nocturnal and early morning pulsatile increases in secretion of adrenocorticotropic hormone (ACTH) by the pituitary, resulting in a diurnal variation of cortisol plasma concentrations [16, 17]. ACTH secretion itself is induced by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), released in the pituitary portal circulation by neurons of the hypothalamic paraventricular nucleus in response to stimulation by catecholaminergic projections or limbic activation, thus integrating both physiological and psychological stressors into the final adrenocortical stress response [18]. In the peripheral circulation, the majority of cortisol is bound to its specific binding protein, transcortin or corticosteroid-binding globulin (CBG), and to albumin [19]. Only free cortisol is biologically active and manifests its pleiotropic homeostatic effects through the glucocorticoid receptor, resulting in mobilization of protein and fatty acid stores for gluconeogenesis, in increased vasomotor tone and fluid retention, and in an anti-inflammatory cytokine environment [20]. Cortisol directly inhibits the release of both ACTH and its hypothalamic secretagogues, an effect that is further fine-tuned by autoregulatory central feedback loops (Fig. 9.1) [16, 21].

Within the first hours of critical illness, plasma cortisol concentrations rapidly rise [22, 23]. In contrast, plasma ACTH concentrations are low, due to reduced nocturnal burst size of ACTH secretion [24, 25]. The secretory ACTH-cortisol feedback relationship does remain present in critical illness, albeit with reduced burst size [24]. This apparent paradox implies a non-ACTH-driven mechanism to maintain high concentrations of cortisol that subsequently feedback-inhibit ACTH release [22]. Reduced cortisol breakdown by A-ring reductases and by 11β-hydroxysteroid dehydrogenase type 2 in the liver and kidneys, respectively, an increase in the free cortisol fraction due to a decrease in CBG and albumin, and direct adrenocortical stimulation by cytokines and the sympathetic nervous system contribute to the maintenance of high free cortisol in the presence of reduced hypothalamic-pituitary output [22, 26]. At the tissue level, critical illness seems to alter the glucocorticoid receptor levels, corticosteroid affinity, and receptor isoform in neutrophils and the liver [27–29]. However, as local concentrations of free cortisol can be altered due to activity of neutrophil elastase and 11β-hydroxysteroid dehydrogenase type 2, investigation in larger samples is necessary to elucidate the resultant effect on local cortisol action [27–30].

Cortisol remains elevated throughout the chronic phase of critical illness, thus resulting in ongoing suppression of ACTH as critical illness persists [24, 25, 31]. Adrenocortical integrity itself appears to be negatively affected when trophic input is insufficient for more than 1 week, as postmortem analyses of adrenal glands in long-stay ICU patients showed a loss of cortical mass, lipid content, and expression of steroidogenic proteins which were not observed in short-stay ICU patients [22, 32]. Of note is that in a longitudinal study measuring cortisol and ACTH in long-stay ICU patients who eventually recovered from critical illness, ACTH levels tended to rise towards the end of ICU stay as cytokine levels dropped [25]. This led the authors to suggest that in the chronic or even recovery phase of critical illness, the role of ACTH in determining cortisol concentrations again increases, though the rate of cortisol metabolism was not taken into account [25].

The question whether the diminished secretory cortisol response to (exogenous) ACTH observed in prolonged critically ill patients identifies adrenal failure requiring treatment, when circulating cortisol is high and cortisol breakdown is reduced, has become highly controversial [31]. Although hypercortisolism in critically ill patients seems appropriate from a hemodynamic perspective and ICU treatments interfering with cortisol synthesis have been shown to increase mortality, the negative impact of inappropriately high cortisol on immune function, wound healing, and nitrogen balance extrapolated from syndromes of chronic hypercortisolism such as Cushing's disease should be taken into account [12, 33, 34]. Reference values for cortisol in critical illness are difficult to define given its association with severity of illness and given the use of therapies in the ICU with impact on corticosteroid homeostasis as summarized in Table 9.1 [25]. Furthermore, given the reduced cortisol metabolism, administration of exogenous corticosteroids could result in much higher cortisol levels than originally anticipated, thus potentially putting a patient population already prone to ICU-acquired weakness (ICUAW) and secondary infections at increased risk for these complications [26].

The concept of critical illness-related corticosteroid insufficiency (CIRCI), a term introduced by the Society of Critical Care Medicine to describe plasma cortisol concentrations that are inadequate relative to the imposed stress, has been extensively investigated in the context of septic shock [35]. Whereas high-dose methylprednisolone in patients with septic shock resulted in worse outcome, lower doses of hydrocortisone (200 mg per day) in patients with septic shock in the context of "relative adrenal insufficiency" led to

faster shock reversal [36–39]. However, neither an association between total cortisol response to exogenous ACTH and survival from sepsis nor a survival benefit of lower doses of corticosteroid treatment was evident in RCTs and meta-analyses [37, 39, 40].

Further insight in the outcome effects of corticosteroid treatment in a prolonged critically ill patient population may be provided by small trials including patients with adult respiratory distress syndrome (ARDS), where methylprednisolone resulted in a reduction of ventilator- and ICU-associated hospitalization days, better hemodynamic parameters, and possibly a small mortality benefit when treatment was initiated within the first week [41, 42]. Unfortunately, the incidence of neuromyopathy in corticosteroid-treated patients was also higher [41]. As recent follow-up studies reported unfavorable long-term morbidity outcomes in ARDS survivors, in particular with respect to subjective and objective physical function, the relationship between ICUAW, long-term weakness, and use of corticosteroids needs to be clarified [5, 33]. The only generally accepted use of corticosteroids in the context of critical illness is the administration of stress doses of hydrocortisone to prevent an Addisonian crisis in those patients with known primary adrenal insufficiency or tertiary adrenal insufficiency as a consequence of long-term corticosteroid therapy at doses equivalent to more than 5 mg of prednisone [43–45]. However, as proposed dosage schemes have been developed assuming that cortisol production in critical illness is increased manifold and do not take into account the reduced cortisol breakdown, updating the dosage regimens might be warranted should a negative impact of corticosteroids on functional outcomes be further supported [26]. Controversy exists about laboratory diagnostic criteria for adrenal insufficiency, leading to highly variable use of corticosteroids in clinical practice. Recent guidelines (Table 9.2) suggest limiting the use of corticosteroids in ICU by stringent clinical criteria but could only assign a low level of recommendation [35, 46]. Given the lack of clear mortality benefit, the indications for corticosteroid administration might be further narrowed should a causal relationship with ICUAW be confirmed. This is also supported by the much lower daily cortisol production (between 30 mg/d and 60 mg/d depending on the degree of inflammation) rate as compared with so-called low-doses of hydrocortisone (200 mg/d) [22].

In contrast to cortisol, the other adrenal steroids, including aldosterone, dehydroepiandrosterone (DHEA), and its sulfated form DHEAS, are low throughout the course of critical illness [47–49]. Increased responsiveness to angiotensin and catecholamines mediated by hypercortisolism maintains vascular tone and fluid balance in spite of low aldosterone levels [31, 37, 49]. In addition to its role as sex steroid precursor, DHEA has an important immune modulatory effect, and it has been suggested that the long-standing imbalance between levels of cortisol and DHEA(S) in prolonged critical illness contributes to the increased susceptibility to infections [3, 47, 48].

Little is known about the evolution of cortisol after critical illness and its impact on long-term prognosis and the post-intensive care syndrome. Should hypercortisolism inappropriately persist after resolution of critical illness, then a multitude of morbidities commonly observed in Cushing syndrome, ranging from muscle weakness and skin atrophy to cardiovascular disease, as well as memory and mood disturbances, can be anticipated [12]. However, a small study in ARDS survivors found basal afternoon cortisol to be within normal ranges, though it was lower in patients with more than one traumatic memory of ICU stay than in patients with maximally one such memory, further stressed by a positive correlation between basal cortisol concentrations and number of traumatic memories [50, 51]. Although in this study basal cortisol at follow-up did not correlate with the incidence of posttraumatic stress disorder (PTSD) and corticosteroid use in ICU

Table 9.2 Current consensus guidelines on the use of corticosteroids in ICU

Indication		Treatment regime	Benefit/risk	Reference
Sepsis	Vasopressor-unresponsive[a] shock	Hydrocortisone 200 mg/day in continuous infusion (10 mg/h), until reversal of vasopressor dependence, tapering	Reversal of shock Dose may be too high	Guideline: [122] In favor: [36, 37, 123] No survival benefit: [40, 124] Dosing remarks: [26]
Respiratory insufficiency	Early severe ARDS[b] Unresolving ARDS[c]	Methylprednisone loading dose 1 mg/kg on day 1, 1 mg/kg/day in continuous infusion on days 2 to 14, 0.5 mg/kg/day on days 15 to 21, 0.25 mg/kg/day on days 22 to 25, 0.125 mg/kg/day on days 26 to 28 (double dosage in unresolving severe ARDS)	Increased number of ventilator- and hospital-free days Improved survival when initiated early No increased infection rate Increased incidence of ICUAW	Guideline: / In favor: [41, 42, 125, 126] No survival benefit: [41, 42, 126]
	Severe bacterial pneumonia	Use not recommended in clinical practice guidelines [127, 128]	Decreased need of MV and reduced number of ventilator-associated and hospitalization days Reduced time to clinical stability Increased rate of hyperglycemia	Guideline: [127, 128] In favor: [129, 130]
	Moderate to severe PJP pneumonia in AIDS	Oral prednisone 40 mg twice a day on days 1 through 5; 40 mg daily on days 6 through; 20 mg daily on days 11 through 21	Reduced mortality and respiratory failure	Guideline: / In favor: [131]
Primary or tertiary adrenal failure[d]	Moderate to severe medical or surgical stress	Moderate to severe stress: 50–100 mg hydrocortisone on day of surgery Critical illness: cfr. Management of septic shock	Prevention of adrenal crisis Dose may be too high	Guideline: [35] In favor: [44] Dosing remarks: [26]

[a]Systolic blood pressure < 90 mm Hg despite fluid resuscitation and vasopressors for more than 1 hour
[b]$P_AO2:F_IO2$ < 200 on positive end-expiratory pressure 10 cm H20 [125]
[c]Less than 1 point reduction in lung injury score by day 7 of ARDS
[d]Diagnosed prior to ICU, or pragmatic assumption in ICU patients on chronic corticosteroids with a daily dosing equivalent to more than 5 mg prednisone

was not included in the analyses, it is of note that in survivors of major cardiac surgery, the risk of PTSD correlated with in-ICU administration of corticosteroids [52, 53]. These studies were methodologically weak, the reported relationships being small at best. Further in-depth research is warranted to assess whether altered glucocorticoid signaling during and after the episode of stress interferes with aversive memory consolidation and retrieval and how corticosteroid administration in ICU modifies this relationship [54]. Like neuropsychiatric outcome, the effects of altered glucocorticoid signaling during and after ICU stay on muscle function are unclear and difficult to investigate, given the impossibility to assess neuromuscular function of patients on admission, practical difficulties associated with muscle force evaluation in ICU, and incomplete knowledge about the pathophysiology of ICUAW and its potential to recover after critical illness [55, 56]. Prospective research and long-term follow-up of clinical outcome parameters should explore these knowledge gaps.

9.3 Growth Hormone Axis

The growth hormone axis or somatotropic axis plays an essential role in the regulation of various metabolic processes. Lipolysis, amino acid transportation into muscle tissue, and hepatic gluconeogenesis are direct effects of growth hormone (GH), but GH also has indirect effects on body growth and anabolism by inducing insulin-like growth factor I (IGF-I) secretion [57]. Growth hormone-releasing hormone (GHRH) and somatostatin act in concert with ghrelin and other GH-releasing peptides (GHRP) to regulate GH secretion from the anterior pituitary [57, 58]. Multiple negative feedback loops are embedded in this axis, of which a direct suppressive effect by IGF-I on the pituitary gland is the most dominant [58, 59]. This complex regulation leads to a pulsatile pattern of GH release with high peaks and almost undetectable interpulse concentrations. IGF-I concentration is more constant, but bioavailability is regulated by different types of IGF-binding proteins (IGFBP) [58, 59]. In circulation, IGF-I is predominantly bound to IGFBP-3 and acid-labile subunit (ALS) to form a large ternary complex, whereas only a small fraction is bound to other smaller IGFBPs in binary complexes that cross the endothelium more easily [59].

In the acute phase of critical illness, stress induces the pituitary to secrete GH with increased pulse frequency and higher peak and baseline GH concentrations. Serum concentrations of IGF-I are low, while the growth hormone receptor appears to be downregulated [59, 60]. Altered serum concentrations of IGFBPs, especially IGFBP-3, ALS, and IGFBP-1, increase IGF-I clearance, which further contributes to low serum IGF-I concentrations [61]. Due to the apparent state of GH resistance, direct effects of GH, such as lipolysis and immune stimulation, are enhanced, whereas indirect effects are suppressed, thereby providing essential substrates to vital organs by inducing catabolism while avoiding costly anabolism.

When a patient does not recover swiftly and enters a state of prolonged critical illness, functionality of the GH axis again dramatically changes. The pulsatile fraction of GH secretion drops although pulse frequency remains high, while interpulse GH concentrations are still elevated [2, 62]. Reduced pulsatility of GH leads to a further reduction in circulating IGF-I concentrations [9, 63]. Low IGF-I concentrations thus are no longer explained by peripheral GH resistance, but rather by a hypothalamic suppression leading to a less active anterior pituitary gland [62, 64]. These low IGF-I concentrations can fur-

ther contribute to muscle wasting and impaired recovery of organ functions by ongoing catabolism [65].

In an attempt to improve anabolism in critically ill patients, various interventions at the level of the GH axis have been investigated in a clinical setting. Recombinant human GH (rhGH) initially appeared promising with several small studies reporting beneficial effects on lean body mass and protein balance [66–68]. However, enthusiasm was countered when a large multicenter randomized controlled trial demonstrated an increased ICU and hospital mortality in prolonged critically ill patients treated with GH [69]. This finding might be caused by supraphysiological dosing of rhGH, especially in the prolonged phase of critical illness when GH sensitivity has recovered, with an increase in toxic side effects such as insulin resistance [70]. Administration of recombinant human IGF-I to critically ill patients could theoretically inhibit protein breakdown. A very small trial demonstrated that a single dose of IGF-I did not induce adverse effects but did not study any efficacy outcome [71]. Combined treatment with GH, IGF-I, and glutamine improved protein balance in two small studies that, however, did not investigate clinical outcome [72, 73]. Treatment with GHRH and/or GHRP might be a more attractive alternative than administering GH or IGF-I, as this restores pulsatile GH secretion as well as increases IGF-I and ternary complex binding proteins [62]. In theory, this intervention is also safer as it maintains negative feedback loops intact with prevention of overstimulation of the GH axis. Co-administration of multiple hypothalamic releasing hormones as pituitary stimulators, including GHRH, GHRP-2, thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH), was able to reduce catabolism and induce anabolism in peripheral tissues [7, 9].

Involvement of the GH axis in post-intensive care syndrome has not been investigated yet, although clues from the literature in other fields seem promising. Consistent with post-intensive care syndrome, symptoms of growth hormone deficiency in adults and IGF-I deficiency in Laron dwarfism include lower muscle mass and weakness, as well as decreased overall well-being and energy [10, 11]. Lower IGF-I concentrations in the first days after surgery have already been associated with postoperative cognitive dysfunction [74]. In addition, IGF-I is a known regulator of muscle stem cell function, whereas impaired regenerative capacity due to stem cell dysfunction has been shown to contribute to long-term persistence of weakness in a pilot study [4, 75]. Chronic hypopituitarism mainly characterized by GH deficiency has been described after traumatic brain injury, but caution is warranted when extrapolating these results, as the dominant pathophysiological mechanism here appears to be anatomical [76]. Whether GH and IGF-I concentrations thus remain disturbed long after critical illness and whether such disturbance would contribute to long-term impairment of muscular, cognitive, and psychological function remain currently unknown.

9.4 Thyroid Axis

The thyroid axis regulates basal metabolic rate, thermogenesis, and lean body mass. The thyroid gland releases its reservoirs of thyroxin (T_4) upon stimulation by thyrotropin (TSH), of which the pulsatile release by the anterior pituitary is under the control of hypothalamic secretion of TRH [77, 78]. T_4 is a hydrophobic prohormone that is carried to its peripheral target sites by thyroxin-binding globulin (TBG) [77, 78]. After cellular uptake through selective monocarboxylate transporters OATP1C1 and MCT8, T_4 is activated by

iodothyronine deiodinases type 1 (D1, expressed in all tissues except the central nervous system) or type 2 (D2, mainly expressed in the skeletal muscle, brain, and thyroid gland) to triiodothyronine (T_3) [79, 80]. T_3 exerts its genomic effects through binding to the thyroid hormone nuclear receptor, which needs to heterodimerize with the retinoid X receptor [79, 81]. An alternative deiodination reaction mediated by iodothyronine deiodinase type 3 (D3) generates reverse T_3 (rT_3), which renders the thyroid hormone inactive [81]. Both circulating and local thyroid hormones exert inhibitory effects on TSH and TRH secretion [3, 81].

Hypoactivity of the thyroid axis, often referred to as the low T_3 syndrome or non-thyroidal illness (NTI), is a well-known phenomenon in ICU patients, the main origin of which shifts from peripheral to additional central involvement throughout the course of critical illness [2, 3, 82].

The acute phase of critical illness is characterized by a decrease in both circulating and tissue T_3 and an increase in rT_3, due to altered peripheral thyroid hormone conversion secondary to increased peripheral activity of D3 and reduced activity of D1 [80, 82–85]. In addition, the lower concentrations of the thyroid hormone-binding proteins as well as the inhibitory effect of free fatty acids and bilirubin on hormone binding, transport, and metabolism have been shown to contribute to the low T_3. Concurrently, concentrations of both total T_4 and TSH are in the low-normal range, although in surgical patients a transient T_4 and TSH surge has been reported [3, 80, 83, 86]. Of note is that, in spite of normal serum TSH concentrations, the pituitary secretory pattern is already altered in this early stage of critical illness as the nocturnal TSH secretory surge was shown to be absent [3]. The constellation of these early changes in thyroid function mimics a typical fasting response and may be in part attributed to it, given the frequently impaired nutrient intake of critically ill patients [82, 87]. This response could thus represent an adaptation to such low availability of nutrients and could be beneficial by decreasing energy expenditure and by improving bacterial killing capacity via high D3 activity within granulocytes [88, 89].

When critical illness is prolonged, pulsatile TSH secretion is dramatically reduced, a phenomenon that could be mediated by suppressive effects of increased somatostatin release, hypercortisolism, and (endogenous or exogenous) dopamine on TRH gene expression [77, 80, 83, 86]. In this phase, plasma concentrations of T_4 are also low apart from the low T_3. At the tissue level, several changes develop that could be regarded as a compensatory response to the decrease in circulating and tissue concentrations of T_3, thus indicating the need for higher thyroid hormone availability [80, 90–92]. These attempts to increase T_3 availability include an upregulation of the thyroid hormone transporter MCT8 in the skeletal muscle, liver, and kidney, local activation of thyroid hormone by increased D2 activity in the muscle and lung, and more selective expression of the active as compared with the inactive thyroid receptor isoform in the liver, as shown in critically ill patients and/or animals [91, 93].

Low concentrations of T_3 and T_4 correlate well with severity of illness and mortality, but it is uncertain whether low thyroid hormone concentrations explain these adverse outcomes or rather reflect an appropriate compensation for critical illness [80, 85, 94, 95]. Clues for the role of altered thyroid function in critical illness can be deduced from the Early versus Late Parenteral Nutrition in Critically Ill patients (EPaNIC) trial, an RCT comparing the effects of early macronutrient restriction (late parenteral nutrition) with full macronutrient provision via provision of early supplemental parenteral nutrition completing insufficient enteral nutrition. In this RCT, the patient group randomized to late parenteral nutrition had better outcome with respect to risk of nosocomial infection

and weakness as well as duration of dependency on intensive care, a finding that coincided with a more pronounced drop of T_4, T_3, and T_3 to rT_3 ratio in the acute phase of illness [96, 97]. Statistical analyses pointed out that positive effects of accentuated peripheral T_3 inactivation were partially negated by concurrently lowered concentrations of T_4 as marker of more pronounced central suppression of thyroid function [87]. However, causality cannot be implied from these findings [87].

Notwithstanding the plausible benefit of a suppressed thyroid axis in the acute phase of critical illness, continued depletion of thyroid input likely contributes to unfavorable outcome in prolonged critically ill patients. Low T_3 concentrations have been correlated with muscle breakdown and with mortality [63, 84]. Support for a causal relationship between deficient levels of thyroid hormones and loss of lean body mass in prolonged ICU stay is provided by the observation that the thyroid axis of critically ill patients can be reactivated by means of thyrotropic secretagogues and that this induces an anabolic response in both muscle and bone [3, 63]. In order to increase T_3 without increasing its inactive metabolite rT_3, the combined administration of TSH and GH secretagogues appeared necessary, possibly depicting an effect of the GH axis on regulation of deiodinase activity [7, 63]. The administration of TRH and a GH secretagogue is conceptually attractive since it does not pose the practical complexities associated with administration of thyroid hormones T_4 and T_3, i.e., the impaired conversion of T_4 to T_3 and the risk of feedback inhibition on TSH inducing hypothyroidism on therapy withdrawal, respectively [7, 63, 83].

In spite of the plausible benefit of reactivated anabolism in prolonged critically ill patients, no formal treatment indications concerning non-thyroidal illness in the ICU have been formulated [95, 98]. As the use of hypothalamic secretagogues remains to be further explored, treatment would encompass the use of thyroxin, which has the aforementioned efficacy issues and failed to show mortality benefit in ICU patients [99, 100]. The distinction between NTI and primary central hypothyroidism, a clear indication for thyroid hormone substitution, is thus relevant but often difficult. The finding of low concentrations of T_3 and T_4 together with an often slightly elevated TSH, an increased T_3 to T_4 ratio, and decreased rT_3 support a diagnosis of central hypothyroidism, which should be treated accordingly [98].

As with the other neuroendocrine axes, the evolution of thyroid hormone and thyrotropin after critical illness is virtually unexplored. The relationship between T_4 and T_3 and several aspects of mood and cognition, even in the euthyroid range, is well known, but its exact regulatory pathways are not fully understood, and evidence on causality between (sub)clinical hypothyroidism and specific cognitive outcomes such as mild cognitive impairment is conflicting [13, 101]. Extrapolation from clinical data is complicated by the unique thyroid axis alterations in critical illness, in particular altered peripheral conversion of T_4. However, the reduced hypothalamic thyrotropic output in prolonged critical illness partly resembles central hypothyroidism. In central hypothyroidism, cognition and mood are negatively affected, and these defects seem to be only partially reversed with T_4 replacement therapy [102, 103]. This finding is an element with potential clinical relevance in ICU survivors given the impaired peripheral conversion to T_3 in the phase of critical illness. Whether the changes in the thyroid axis persist and may contribute to long-term adverse outcome of ICU survivors should be further investigated.

9.5 Gonadotropic Axis

The gonadotropic axes play an age- and gender-dependent physiological role in growth, sexual differentiation, and reproduction. In analogy to the aforementioned neuroendocrine axes, the hypothalamus secretes GnRH in a pulsatile fashion, stimulating the pituitary gonadotropes to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which act in concert to regulate sex steroid production and reproduction [3]. Under physiological conditions, the main production sites of the sex hormones are the testes and ovaries, though steroidogenesis by the adrenals and the liver with subsequent peripheral aromatization also contributes [3, 104]. In men, LH stimulates the production of testosterone and androstenedione by the testicular Leydig cells, whereas spermatogenesis requires the combined action of FSH and testosterone on Sertoli cells [3]. In women, LH also mediates ovarian androgen production, whereas FSH orchestrates ovarian aromatization of androgens to estrogens [3]. Sex steroids exert a negative feedback on GnRH and gonadotropin secretion [105]. Other centrally acting inhibitors include leptin, prolactin, corticotropin-releasing hormone, and inhibin [105].

In men, the acute phase of critical illness is hallmarked by a rapid decline in testosterone to prepubertal concentrations, even despite a transient increase in LH and thus prior to a decrease in LH secretion, in which increased testosterone metabolism and inhibition of Leydig cells by cytokines and reduced IGF-1 signalling could play a role [3, 105]. In contrast, serum estrogen levels are increased due to increased peripheral aromatization [105]. In the short term, the decrease in anabolic androgens could be viewed as an attempt to reduce energy consumption and conserve substrates for more vital functions. As critical illness persists, pulsatility of LH secretion is lost and LH concentrations are low [105]. In this phase, testosterone concentrations decrease further, often becoming undetectable. Both relatively low and high estrogen concentrations have been reported. As testosterone is the most potent endogenous anabolic steroid, sustained low concentrations could have important implications with regard to the hypercatabolism of critical illness. Though research in critically ill women is limited and samples mainly consist of postmenopausal patients, LH and FSH concentrations seem to be reduced.

Several factors may contribute to the profound hypogonadism, including endogenous or exogenous dopamine, opiates, maintained bioactive estradiol, prolonged local increases in cytokines at the level of the brain, and increased HPA axis activation [1, 3]. Glucocorticoids cause reduced secretion of GnRH and inhibit gonadal function and responsiveness to the effects of the gonadotropic hormones [1]. The complicated interactions affecting the gonadotropic axis are further illustrated by the fact that the hypogonadotropic hypogonadism of prolonged critical illness cannot (or only transiently) be restored by isolated administration of GnRH but instead requires a combination of GHRP-2 and TRH infusion concurrently with GnRH pulses [7, 8]. The positive metabolic alterations in critically ill men associated with this combined intervention seem to warrant further investigation, though reduced commercial availability of these secretagogues has obstructed research initiatives. Alternative strategies reactivating the gonadotropic axis in order to restore anabolism, including testosterone substitution as well as administration of the more selective anabolic steroid oxandrolone, failed to show benefit in RCTs conducted in critically ill men, and a negative effect of testosterone on immune function has been suggested by animal studies [3, 106, 107].

9.6 Lactotropic Axis

Prolactin functions as a stress hormone, serves additional functions during breastfeeding, and is also presumed to have immune-enhancing properties [3]. The physiological diurnal variation in prolactin stems from pulsatile release by the pituitary, though the regulatory aspects are not fully understood [108].

In the context of critical illness, prolactin rises acutely, possibly through the effects of vasoactive intestinal peptide, oxytocin, (endogenous or exogenous) dopamine, and cytokines on the pituitary [3]. Its function is incompletely understood but may involve regulation of immune system activation [3]. In the prolonged phase of critical illness, mean nocturnal prolactin concentrations have been shown to be low-normal, but its pulsatile release appeared to be low with absence of the nocturnal surge [108]. Although it has been suggested that blunted prolactin secretion could contribute to imbalanced immune function, the clinical relevance of hypoprolactinemia in prolonged critical illness is unclear [3].

Conclusions

Critical illness-induced endocrinopathy has a biphasic pattern. Neuroendocrine alterations in the acute phase safeguard energy and substrate provision for the vital organs and are therefore considered adaptive. The characteristic neuroendocrine disturbances in the chronic phase, however, contribute to the ongoing hypercatabolism and therefore are presumed detrimental. Whether the neuroendocrine changes should be treated during critical illness remains controversial, but administration of hypothalamic releasing factors to prolonged critically ill patients appeared promising. Currently, it is unclear whether the neuroendocrine disturbances persist after critical illness. Nevertheless, evidence from other fields suggests a potential role of neuroendocrine disturbances in long-term impairment of physical and cognitive functioning.

References

1. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 1992;267(9):1244–52.
2. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab. 1998;83(6):1827–34.
3. Vanhorebeek I, Langouche L, Van den Berghe G. Endocrine aspects of acute and prolonged critical illness. Nat Clin Pract Endocrinol Metab. 2006;2(1):20–31.
4. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.
5. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
6. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787–94.
7. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Iranmanesh A, et al. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. Clin Endocrinol. 2002;56(5):655–69.
8. van den Berghe G, Weekers F, Baxter RC, Wouters P, Iranmanesh A, Bouillon R, et al. Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. J Clin Endocrinol Metab. 2001;86(7):3217–26.

9. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab. 1999;84(4):1311–23.
10. Kargi AY, Merriam GR. Diagnosis and treatment of growth hormone deficiency in adults. Nat Rev Endocrinol. 2013;9(6):335–45.
11. Puche JE, Castilla-Cortázar I. Human conditions of insulin-like growth factor-I (IGF-I) deficiency. J Transl Med. 2012;10:224.
12. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913–27.
13. Parsaik AK, Singh B, Roberts RO, Pankratz S, Edwards KK, Geda YE, et al. Hypothyroidism and risk of mild cognitive impairment in elderly persons: a population-based study. JAMA Neurol. 2014;71(2):201–7.
14. Pandharipande PP, Girard TD, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med. 2014;370(2):185–6.
15. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20.
16. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259–84.
17. Hellman L, Nakada F, Curti J, Weitzman ED, Kream J, Roffwarg H, et al. Cortisol is secreted episodically by normal man. J Clin Endocrinol Metab. 1970;30(4):411–22.
18. Kovács KJ. CRH: the link between hormonal-, metabolic- and behavioral responses to stress. J Chem Neuroanat. 2013;54:25–33.
19. Hammond GL. Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. J Endocrinol. 2016;230(1):R13–25.
20. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol. 2013;132(5):1033–44.
21. Dorin RI, Ferries LM, Roberts B, Qualls CR, Veldhuis JD, Lisansky EJ. Assessment of stimulated and spontaneous adrenocorticotropin secretory dynamics identifies distinct components of cortisol feedback inhibition in healthy humans. J Clin Endocrinol Metab. 1996;81(11):3883–91.
22. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, et al. Reduced cortisol metabolism during critical illness. N Engl J Med. 2013;368(16):1477–88.
23. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab. 1995;80(4):1238–42.
24. Boonen E, Meersseman P, Vervenne H, Meyfroidt G, Guïza F, Wouters PJ, et al. Reduced nocturnal ACTH-driven cortisol secretion during critical illness. Am J Physiol Endocrinol Metab. 2014;306(8):E883–92.
25. Vassiliadi DA, Dimopoulou I, Tzanela M, Douka E, Livaditi O, Orfanos SE, et al. Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcome. J Clin Endocrinol Metab. 2014;99(12):4471–80.
26. Boonen E, Van den Berghe G. Cortisol metabolism in critical illness: implications for clinical care. Curr Opin Endocrinol Diabetes Obes. 2014;21(3):185–92.
27. Siebig S, Meinel A, Rogler G, Klebl E, Wrede CE, Gelbmann C, et al. Decreased cytosolic glucocorticoid receptor levels in critically ill patients. Anaesth Intensive Care. 2010;38(1):133–40.
28. van den Akker EL, Koper JW, Joosten K, de Jong FH, Hazelzet JA, Lamberts SW, et al. Glucocorticoid receptor mRNA levels are selectively decreased in neutrophils of children with sepsis. Intensive Care Med. 2009;35(7):1247–54.
29. Peeters RP, Hagendorf A, Vanhorebeek I, Visser TJ, Klootwijk W, Mesotten D, et al. Tissue mRNA expression of the glucocorticoid receptor and its splice variants in fatal critical illness. Clin Endocrinol. 2009;71(1):145–53.
30. Perogamvros I, Ray DW, Trainer PJ. Regulation of cortisol bioavailability--effects on hormone measurement and action. Nat Rev Endocrinol. 2012;8(12):717–27.
31. Boonen E, Bornstein SR, Van den Berghe G. New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol. 2015;3(10):805–15.
32. Boonen E, Langouche L, Janssens T, Meersseman P, Vervenne H, De Samblanx E, et al. Impact of duration of critical illness on the adrenal glands of human intensive care patients. J Clin Endocrinol Metab. 2014;99(11):4214–22.

33. Fletcher SN, Kennedy DD, Ghosh IR, Misra VP, Kiff K, Coakley JH, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. Crit Care Med. 2003;31(4):1012–6.
34. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med. 2007;35(4):1012–8.
35. Pastores SM, Annane D, Rochwerg B, ESICM atCGTFoSa. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med. 2018;46(1):146–8.
36. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283(8):1038–45.
37. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA. 2009;301(22):2362–75.
38. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. N Engl J Med. 1984;311(18):1137–43.
39. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018;378:797.
40. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111–24.
41. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354(16):1671–84.
42. Meduri GU, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med. 2008;34(1):61–9.
43. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003;348(8):727–34.
44. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA. 2002;287(2):236–40.
45. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Arch Surg. 2008;143(12):1222–6.
46. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
47. Hässig A, Wen-Xi L, Stampfli K. Stress-induced suppression of the cellular immune reactions: on the neuroendocrine control of the immune system. Med Hypotheses. 1996;46(6):551–5.
48. Ebeling P, Koivisto VA. Physiological importance of dehydroepiandrosterone. Lancet. 1994;343(8911):1479–81.
49. Findling JW, Waters VO, Raff H. The dissociation of renin and aldosterone during critical illness. J Clin Endocrinol Metab. 1987;64(3):592–5.
50. Schelling G. Effects of stress hormones on traumatic memory formation and the development of posttraumatic stress disorder in critically ill patients. Neurobiol Learn Mem. 2002;78(3):596–609.
51. Hauer D, Weis F, Krauseneck T, Vogeser M, Schelling G, Roozendaal B. Traumatic memories, posttraumatic stress disorder and serum cortisol levels in long-term survivors of the acute respiratory distress syndrome. Brain Res. 2009;1293:114–20.
52. Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. J Thorac Cardiovasc Surg. 2006;131(2):277–82.
53. Kok L, Hillegers MH, Veldhuijzen DS, Cornelisse S, Nierich AP, van der Maaten JM, et al. The effect of dexamethasone on symptoms of posttraumatic stress disorder and depression after cardiac surgery and intensive care admission: longitudinal follow-up of a randomized controlled trial. Crit Care Med. 2016;44(3):512–20.
54. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:15057.

55. Jolley SE, Bunnell AE, Hough CL. ICU-acquired weakness. Chest. 2016;150(5):1129–40.
56. Dettling-Ihnenfeldt DS, Wieske L, Horn J, Nollet F, van der Schaaf M. Functional recovery in patients with and without intensive care unit-acquired weakness. Am J Phys Med Rehabil. 2017;96(4):236–42.
57. Ho KK, O'Sullivan AJ, Hoffman DM. Metabolic actions of growth hormone in man. Endocr J. 1996;43(Suppl):S57–63.
58. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19(6):717–97.
59. Mesotten D, Van den Berghe G. Changes within the GH/IGF-I/IGFBP axis in critical illness. Crit Care Clin. 2006;22(1):17–28.
60. Defalque D, Brandt N, Ketelslegers JM, Thissen JP. GH insensitivity induced by endotoxin injection is associated with decreased liver GH receptors. Am J Phys. 1999;276(3 Pt 1):E565–72.
61. Baxter RC. Changes in the IGF-IGFBP axis in critical illness. Best Pract Res Clin Endocrinol Metab. 2001;15(4):421–34.
62. Van den Berghe G, de Zegher F, Veldhuis JD, Wouters P, Awouters M, Verbruggen W, et al. The somatotropic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion. J Clin Endocrinol Metab. 1997;82(2):590–9.
63. Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab. 1998;83(2):309–19.
64. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Veldhuis JD. A paradoxical gender dissociation within the growth hormone/insulin-like growth factor I axis during protracted critical illness. J Clin Endocrinol Metab. 2000;85(1):183–92.
65. Hadley JS, Hinds CJ. Anabolic strategies in critical illness. Curr Opin Pharmacol. 2002;2(6):700–7.
66. Pichard C, Kyle U, Chevrolet JC, Jolliet P, Slosman D, Mensi N, et al. Lack of effects of recombinant growth hormone on muscle function in patients requiring prolonged mechanical ventilation: a prospective, randomized, controlled study. Crit Care Med. 1996;24(3):403–13.
67. Koea JB, Breier BH, Douglas RG, Gluckman PD, Shaw JH. Anabolic and cardiovascular effects of recombinant human growth hormone in surgical patients with sepsis. Br J Surg. 1996;83(2):196–202.
68. Gamrin L, Essén P, Hultman E, McNurlan MA, Garlick PJ, Wernerman J. Protein-sparing effect in skeletal muscle of growth hormone treatment in critically ill patients. Ann Surg. 2000;231(4):577–86.
69. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999;341(11):785–92.
70. Ruokonen E, Takala J. Dangers of growth hormone therapy in critically ill patients. Curr Opin Clin Nutr Metab Care. 2002;5(2):199–209.
71. Yarwood GD, Ross RJ, Medbak S, Coakley J, Hinds CJ. Administration of human recombinant insulin-like growth factor-I in critically ill patients. Crit Care Med. 1997;25(8):1352–61.
72. Carroll PV, Jackson NC, Russell-Jones DL, Treacher DF, Sönksen PH, Umpleby AM. Combined growth hormone/insulin-like growth factor I in addition to glutamine-supplemented TPN results in net protein anabolism in critical illness. Am J Physiol Endocrinol Metab. 2004;286(1):E151–7.
73. Umpleby AM, Carroll PV, Russell-Jones DL, Treacher DF, Jackson NC. Glutamine supplementation and GH/IGF-I treatment in critically ill patients: effects on glutamine metabolism and protein balance. Nutrition. 2002;18(2):127–9.
74. Jiang J, Chen Z, Liang B, Yan J, Zhang Y, Jiang H. Insulin-like growth factor-1 and insulin-like growth factor binding protein 3 and risk of postoperative cognitive dysfunction. Springerplus. 2015;4:787.
75. Pirskanen A, Kiefer JC, Hauschka SD. IGFs, insulin, Shh, bFGF, and TGF-beta1 interact synergistically to promote somite myogenesis in vitro. Dev Biol. 2000;224(2):189–203.
76. Klose M, Feldt-Rasmussen U. Chronic endocrine consequences of traumatic brain injury – what is the evidence? Nat Rev Endocrinol. 2018;14(1):57–62.
77. Fliers E, Wiersinga WM, Swaab DF. Physiological and pathophysiological aspects of thyrotropin-releasing hormone gene expression in the human hypothalamus. Thyroid. 1998;8(10):921–8.
78. Fliers E, Unmehopa UA, Alkemade A. Functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and pituitary gland. Mol Cell Endocrinol. 2006;251(1–2):1–8.
79. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23(1):38–89.
80. Mebis L, Van den Berghe G. Thyroid axis function and dysfunction in critical illness. Best Pract Res Clin Endocrinol Metab. 2011;25(5):745–57.

81. Van den Berghe G. On the neuroendocrinopathy of critical illness. Perspectives for feeding and novel treatments. Am J Respir Crit Care Med. 2016;194(11):1337–48.
82. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456–65.
83. Mebis L, van den Berghe G. The hypothalamus-pituitary-thyroid axis in critical illness. Neth J Med. 2009;67(10):332–40.
84. Peeters RP, van der Geyten S, Wouters PJ, Darras VM, van Toor H, Kaptein E, et al. Tissue thyroid hormone levels in critical illness. J Clin Endocrinol Metab. 2005;90(12):6498–507.
85. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab. 2003;88(7):3202–11.
86. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab. 1997;82(12):4032–6.
87. Langouche L, Vander Perre S, Marques M, Boelen A, Wouters PJ, Casaer MP, et al. Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its relation with outcome: a randomized, controlled clinical study. J Clin Endocrinol Metab. 2013;98(3):1006–13.
88. Boelen A, Boorsma J, Kwakkel J, Wieland CW, Renckens R, Visser TJ, et al. Type 3 deiodinase is highly expressed in infiltrating neutrophilic granulocytes in response to acute bacterial infection. Thyroid. 2008;18(10):1095–103.
89. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev. 2011;32(5):670–93.
90. Mebis L, Langouche L, Visser TJ, Van den Berghe G. The type II iodothyronine deiodinase is upregulated in skeletal muscle during prolonged critical illness. J Clin Endocrinol Metab. 2007;92(8):3330–3.
91. Mebis L, Paletta D, Debaveye Y, Ellger B, Langouche L, D'Hoore A, et al. Expression of thyroid hormone transporters during critical illness. Eur J Endocrinol. 2009;161(2):243–50.
92. Thijssen-Timmer DC, Peeters RP, Wouters P, Weekers F, Visser TJ, Fliers E, et al. Thyroid hormone receptor isoform expression in livers of critically ill patients. Thyroid. 2007;17(2):105–12.
93. Ma SF, Xie L, Pino-Yanes M, Sammani S, Wade MS, Letsiou E, et al. Type 2 deiodinase and host responses of sepsis and acute lung injury. Am J Respir Cell Mol Biol. 2011;45(6):1203–11.
94. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med. 1995;23(1):78–83.
95. Vaughan GM, Pruitt BA. Thyroid function in critical illness and burn injury. Semin Nephrol. 1993;13(4):359–70.
96. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
97. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621–9.
98. Van den Berghe G. Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin N Am. 2003;32(2):385–410.
99. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab. 1986;63(1):1–8.
100. Becker RA, Vaughan GM, Ziegler MG, Seraile LG, Goldfarb IW, Mansour EH, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med. 1982;10(12):870–5.
101. Wu T, Flowers JW, Tudiver F, Wilson JL, Punyasavatsut N. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. BMC Pediatr. 2006;6:12.
102. Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Nat Rev Endocrinol. 2014;10(3):164–74.
103. Yamada M, Mori M. Mechanisms related to the pathophysiology and management of central hypothyroidism. Nat Clin Pract Endocrinol Metab. 2008;4(12):683–94.
104. Mechanick JI, Nierman DM. Gonadal steroids in critical illness. Crit Care Clin. 2006;22(1): 87–103.. vii
105. Spratt DI. Altered gonadal steroidogenesis in critical illness: is treatment with anabolic steroids indicated? Best Pract Res Clin Endocrinol Metab. 2001;15(4):479–94.
106. Bulger EM, Jurkovich GJ, Farver CL, Klotz P, Maier RV. Oxandrolone does not improve outcome of ventilator dependent surgical patients. Ann Surg. 2004;240(3):472–8; discussion 8-80.

107. Gervasio JM, Dickerson RN, Swearingen J, Yates ME, Yuen C, Fabian TC, et al. Oxandrolone in trauma patients. Pharmacotherapy. 2000;20(11):1328–34.
108. Van den Berghe G, de Zegher F, Veldhuis JD, Wouters P, Gouwy S, Stockman W, et al. Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone-secretagogues. Clin Endocrinol. 1997;47(5):599–612.
109. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. Crit Care Med. 1996;24(9):1580–90.
110. Van den Berghe G, de Zegher F, Wouters P, Schetz M, Verwaest C, Ferdinande P, et al. Dehydroepiandrosterone sulphate in critical illness: effect of dopamine. Clin Endocrinol. 1995;43(4):457–63.
111. Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med. 1995;333(25):1688–94.
112. Vinclair M, Broux C, Faure P, Brun J, Genty C, Jacquot C, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. Intensive Care Med. 2008;34(4):714–9.
113. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310(22):1415–21.
114. Lamberts SW, Bons EG, Bruining HA, de Jong FH. Differential effects of the imidazole derivatives etomidate, ketoconazole and miconazole and of metyrapone on the secretion of cortisol and its precursors by human adrenocortical cells. J Pharmacol Exp Ther. 1987;240(1):259–64.
115. Eigler T, Ben-Shlomo A. Somatostatin system: molecular mechanisms regulating anterior pituitary hormones. J Mol Endocrinol. 2014;53(1):R1–19.
116. Christy NP. Pituitary-adrenal function during corticosteroid therapy. Learning to live with uncertainty. N Engl J Med. 1992;326(4):266–7.
117. Whirledge S, Cidlowski JA. Glucocorticoids, stress, and fertility. Minerva Endocrinol. 2010;35(2):109–25.
118. Chidakel AR, Zweig SB, Schlosser JR, Homel P, Schappert JW, Fleckman AM. High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. J Endocrinol Investig. 2006;29(2):136–40.
119. Malik KJ, Wakelin K, Dean S, Cove DH, Wood PJ. Cushing's syndrome and hypothalamic-pituitary adrenal axis suppression induced by medroxyprogesterone acetate. Ann Clin Biochem. 1996;33. (Pt 3:187–9.
120. Rhodin A, Stridsberg M, Gordh T. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. Clin J Pain. 2010;26(5):374–80.
121. Sherman SI, Gopal J, Haugen BR, Chiu AC, Whaley K, Nowlakha P, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. N Engl J Med. 1999;340(14):1075–9.
122. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228.
123. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med. 1999;27(4):723–32.
124. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2015;41(7):1220–34.
125. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest. 2007;131(4):954–63.
126. Annane D, Sébille V, Bellissant E, Group G-I-S. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med. 2006;34(1):22–30.
127. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect. 2011;17(Suppl 6):E1–59.
128. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
129. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2015;385(9977):1511–8.
130. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015;313(7):677–86.
131. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection. Cochrane Database Syst Rev. 2006;(3):CD006150.

Post-ICU Diabetes

Yasmine Ali Abdelhamid and Adam Deane

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_10

Learning Objectives

This chapter summarises the pathophysiology of stress hyperglycaemia during critical illness, updates evidence that patients post critical illness frequently develop diabetes, outlines putative mechanisms underlying this 'post-intensive care unit (ICU) diabetes' and discusses the potential roles for screening and treatment to prevent post-ICU diabetes and its complications.

10.1 Introduction

Stress hyperglycaemia describes the phenomenon of hyperglycaemia that occurs in critically ill patients in whom glucose tolerance was previously normal and initially resolves following recovery [1]. For this reason, stress hyperglycaemia traditionally has not been considered to have an adverse impact on long-term health [1]. However, it has been recently recognised that there are strong associations between stress hyperglycaemia during intensive care unit (ICU) admission and the subsequent development of type 2 diabetes in ICU survivors [2]. This phenomenon could therefore be referred to as 'post-ICU diabetes.'

An increased risk of diabetes in this group may be of particular importance as survivors of ICU frequently experience long-term complications such as sensorimotor peripheral neuropathy, autonomic neuropathy and nephropathy [3–6], all of which have the potential to be exacerbated by the development of concomitant diabetes. Screening for diabetes is relatively inexpensive and can be performed in numerous health-care settings. Thus, an opportunity may exist for screening and follow-up of patients with stress hyperglycaemia to reduce progression to diabetes and prevent complications associated with long-term hyperglycaemia.

10.2 Stress Hyperglycaemia

'Stress hyperglycaemia' is defined as a blood glucose that, in health, would lead to a diagnosis of diabetes but initially resolves with resolution of the critical illness [7, 8]. It is accepted that stress hyperglycaemia occurs frequently – up to 50% of critically ill patients are hyperglycaemic within 48 hours of ICU admission [8]. The prevalence of stress hyperglycaemia depends upon the glucose threshold used, the population studied and whether patients who have unrecognised type 2 diabetes are excluded from estimates [8]. Studies to identify patients with unrecognised diabetes on hospital admission using glycated haemoglobin (HbA_{1c}) measurements reveal up to 15% of patients have unrecognised diabetes [9]. Nevertheless, even when patients with previously unrecognised diabetes are excluded from estimates, stress hyperglycaemia occurs frequently during critical illness [8].

The pathophysiology of stress hyperglycaemia involves a complex interplay between patient predisposition, the physiological changes associated with critical illness and specific treatments administered in the ICU (Table 10.1). The initial mechanistic studies of stress hyperglycaemia were conducted in war zones. These included blood sampling in soldiers with major injuries and hypovolaemic shock, which identified that the rise in serum insulin in response to the hyperglycaemia was inadequate, particularly as injury severity increased [10]. Insulin secretion was thought to be attenuated due to effects of counter-regulatory hormones on islet cells [10].

Table 10.1 Causes of stress hyperglycaemia in critical illness

Individual patient predisposition	ICU treatments	Physiological changes due to critical illness
Insulin resistance Pancreatic β-cell reserve	Total parenteral nutrition Enteral nutrition Vasopressors Glucocorticoids Dextrose	Increased counter-regulatory hormones (glucagon, cortisol, catecholamines) Inflammatory cytokines (TNF-α, IL-1, IL-6) alter insulin receptor signalling Increased lipolysis: circulating free fatty acids alter insulin receptor signalling

Patient predisposition, physiological changes during critical illness and treatments administered in the ICU can all contribute to the development of stress hyperglycaemia
ICU intensive care unit, *TNF* tumour necrosis factor, *IL* interleukin

It is now considered that the pathogenesis of stress hyperglycaemia is predominately a state of insulin resistance coupled with relative insulin deficiency (insufficient plasma insulin levels to meet demand) [1]. The stress response to critical illness initiates significant activation of inflammatory mediators and a rise in counter-regulatory hormones, both of which increase hepatic gluconeogenesis and drive insulin resistance. Insulin resistance results largely from post-receptor insulin signalling defects in glucose transporters type 4 (GLUT-4) leading to reduced glucose uptake in insulin-sensitive tissues (liver, muscle and fat) [11]. Muscle glycogen storage is also impaired in stress hyperglycaemia [1].

Whether stress hyperglycaemia *per se* is harmful or an epiphenomenon of illness severity is uncertain. During critical illness, stress hyperglycaemia is a known marker of illness severity and the degree of hyperglycaemia is strongly associated with mortality, especially in patients without a history of diabetes [8, 12]. However, there is no conclusive evidence proving this is a causative association. Whilst there is likely to be some concentration at which hyperglycaemia will be harmful, 'mild' stress hyperglycaemia may represent an epiphenomenon [13] or even an adaptive physiological response to critical illness that augments cellular glucose uptake in non-insulin-dependent tissues (such as the nervous system, bone marrow and the reticuloendothelial system), in the setting of the diminished microvascular flow frequently associated with critical illness [14]. The latter hypothesis is supported by the NICE-SUGAR trial. Within this landmark multi-centre trial, tight control of stress hyperglycaemia with intensive insulin therapy (4.4–6.1 mmol/L) when compared to standard care (6–10 mmol/L) increased mortality [15].

10.3 Stress Hyperglycaemia, Prediabetes and Type 2 Diabetes: A Continuum?

It is biologically plausible that critical illness also unmasks latent insulin resistance and/or impaired pancreatic β-cell secretory function in a proportion of susceptible patients [16]. Accordingly, stress hyperglycaemia may identify a cohort at greater risk of subsequent diabetes, even years after survival from critical illness.

Transient hyperglycaemia which occurs in other contexts of physiological 'stress' (i.e. not critical illness) can predict the subsequent development of type 2 diabetes. For example, whilst gestational diabetes was once considered to be a temporary disorder of

pregnancy, it is now well recognised that gestational diabetes strongly predicts the development of type 2 diabetes [17–19]. Screening programmes have been widely implemented postpartum for women with gestational diabetes in order to identify prediabetes and type 2 diabetes early and thereby reduce complications [20, 21].

Furthermore, a number of epidemiological studies have reported an association between hyperglycaemia during hospitalisation that does not involve admission to ICU and the subsequent development of type 2 diabetes (Table 10.2) [22–25]. The most externally valid of these studies to the critical care environment was a retrospective data-linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland [22]. The 3-year risk of developing diabetes for patients who were hyperglycaemic (blood glucose >11 mmol/L) was 10% compared to 2.3% for all patients requiring emergency admission [22].

The mechanisms which underlie progressive glucose intolerance and the development of prediabetes or post-ICU diabetes are likely to be complex and have been infrequently studied (Fig. 10.1). It is plausible that stress hyperglycaemia during ICU identifies those patients with pre-existing impaired β-cell reserve and insulin resistance, but it is possible that critical illness itself accelerates these abnormalities. If insulin resistance persists following critical illness, it is likely to contribute to the development of post-ICU diabetes [26]. The hyperglycaemia which occurs in type 2 diabetes typically results from progressive insulin resistance which develops over years and contributes to ensuing beta-cell secretory defect [27]. However, the insulin resistance of critical illness occurs rapidly, as a result of a dramatic rise in counter-regulatory hormones and inflammatory mediators [1]. Whether insulin resistance persists following critical illness in patients who experienced stress hyperglycaemia and the magnitude of any such persisting insulin resistance have never been evaluated.

In addition to persisting insulin resistance, a number of other mechanisms may be implicated. In health, the gastrointestinal tract plays a key role in the modulation of postprandial glycaemic excursions, with postprandial glycaemia dependent largely on both the rate of gastric emptying and the incretin enterohormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [28]. Loss of postprandial glycaemic control is frequently the first sign of disordered glycaemic control in those that develop type 2 diabetes [29], and postprandial hyperglycaemia has the capacity to contribute to the development of diabetes via glucose toxicity to pancreatic β-cells [27]. The 'incretin effect' describes the increased insulin release following enteral glucose administration when compared with iso-glycaemic intravenous glucose administration [28]. GLP-1 and GIP, which are secreted by the intestine in response to food ingestion, are responsible for the incretin effect and account for up to 70% of the total insulin response to oral glucose in health [30]. There is emerging evidence that the incretin effect is acutely diminished during critical illness, although whether this simply represents attenuated secretion of GIP and GLP-1 or more complex pathophysiology, such as reduced insulinotropic effects of GIP and GLP-1 in the critically ill, remains unknown [31–34]. It should be recognised that measurement of the incretin effect after intragastric administration of nutrient in the critically ill is biased toward a diminished incretin effect: this is because secretion of GIP and GLP-1 are dependent on the rate of gastric emptying [35], and gastric emptying is frequently delayed during critical illness [36]. It is unclear whether attenuation of the incretin effect persists after resolution of critical illness.

The role of gastric dysmotility in the development of post-ICU diabetes has also never been studied. Gastric dysmotility occurs frequently during critical illness [36, 37], but limited data exist about gastric emptying as patients recover [6]. Rapid gastric emptying can lead to larger postprandial glycaemic excursions and may be implicated in the

Table 10.2 Conditions in which stress hyperglycaemia has been found to predict incident diabetes in adult patients outside the ICU setting

Condition	Study design and location	Cohort size	SH definition	Method used to diagnose incident diabetes	Duration of follow-up	Risk of incident diabetes
Hospital admission via emergency department [22]	Multi-centre, RC, Scotland	86,634	Admission BG ≥11.1 mmol/L	Record in national diabetes register (>99% capture rate)	3 years	Incidence in SH: 9.9% (95% CI 9.2–10.6) vs control: <1%
Gestational diabetes [17–19]	Typically multi-centre, either RC or PC studies	Up to 659,164 per study	Various consensus criteria	Annual OGTT	Up to 20 years	Relative risk 7.43 (95% CI 4.79–11.51) from meta-analysis
Myocardial infarction [23]	Multi-centre, RC, United States	10,499	Admission BG ≥7.8 mmol/L	Diagnostic codes, medication prescriptions and/or HbA_{1c} ≥6.5%	6 months	Incidence in SH: 11.8% vs control: 5.1%; odds ratio 2.56 (95% CI 2.15–3.06)
Pneumonia requiring hospitalisation [24]	Multi-centre, PC, Canada	3145	Admission BG ≥11.1 mmol/L	Physician insurance claims and/or hospital diagnostic codes	5 years	Incidence in SH: 47% vs control: 6%; adjusted hazard ratio 11.43 (95% CI 7.50–17.42)
Stroke [25]	Single centre, PC, England	62	Admission BG 6.1–17 mmol/L and no history of diabetes	OGTT	3 months	Incidence 21%, no control group

The methods used to exclude baseline unrecognised diabetes differed among studies
SH stress hyperglycaemia, *RC* retrospective cohort, *BG* blood glucose, *CI* confidence interval, *PC* prospective cohort, *OGTT* oral glucose tolerance test, HbA_{1c} glycated haemoglobin

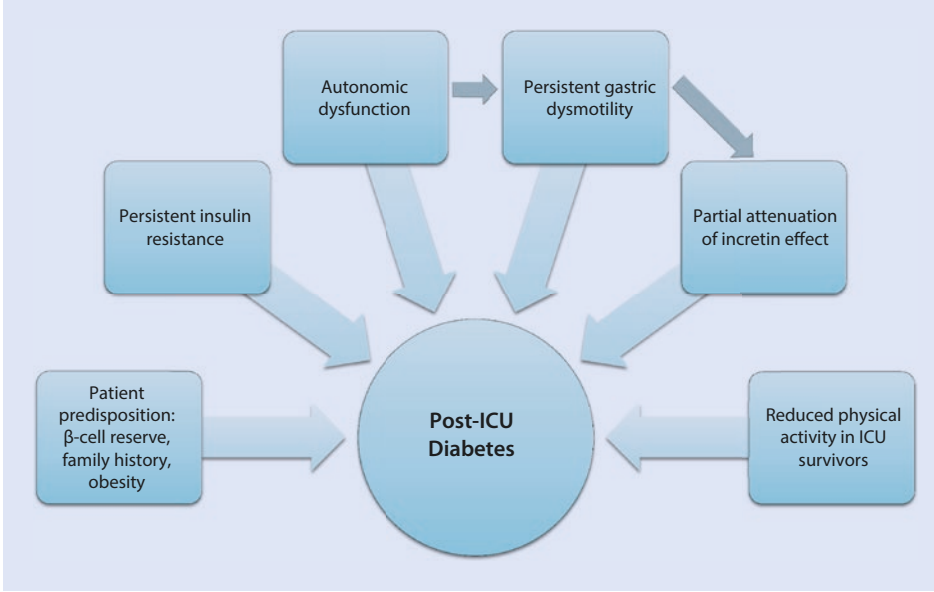


Fig. 10.1 Summary of postulated mechanisms contributing to the development of post-ICU diabetes. A combination of predisposing factors in the patient and physiological changes associated with critical illness may be implicated

pathogenesis of type 2 diabetes [38–40], but delayed gastric emptying can also potentially contribute to hyperglycaemia via a reduction in the incretin effect [41]. Therefore, persistent gastric dysmotility has the potential to contribute to persistent glucose intolerance following critical illness.

Additional mechanisms that may predispose to post-ICU diabetes and warrant further evaluation include the reduction in physical activity and autonomic dysfunction, both of which are reported to occur frequently in survivors of ICU [42, 43]. Physical inactivity and autonomic dysfunction have the capacity to worsen glycaemia and facilitate the earlier development of microvascular complications associated with diabetes [44, 45]. Finally, critically ill patients who experience stress hyperglycaemia are reported to more frequently have a family history of diabetes and a higher body mass index on admission to ICU than critically ill patients with normal glucose tolerance [46, 47]. This suggests that well-accepted risk factors of type 2 diabetes, such as obesity and family history, may also play a key role in the development of post-ICU diabetes.

10.4 Evidence that Stress Hyperglycaemia Predicts Type 2 Diabetes After Critical Illness

The question of whether stress hyperglycaemia identifies survivors of critical illness at increased risk of subsequently developing diabetes has been the subject of a number of retrospective and prospective controlled cohort studies [22, 46–49] and a meta-analysis [2]. The original studies used different methods to determine the risk of incident diabetes and employed various definitions of stress hyperglycaemia (Table 10.3). Two of the prospective cohort studies were conducted in a single centre in Croatia and tested patients

Table 10.3 Summary of studies examining the risk of incident prediabetes and diabetes in survivors of critical illness who experienced stress hyperglycaemia

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Single-centre, PC, Croatia [46]	1029 medical ICU patients with no history of steroid use, pancreatitis, disturbed glucose metabolism or other endocrine disorder	Venous BG in ICU >7.7 mmol/L measured twice per day with point-of-care blood gas analyser	(a) Annual OGTT for 5 years[a] (b) History; OGTT 4–6 weeks after discharge	591	Relative risk 2.3 (95% CI 1.6–3.4)	Relative risk 5.6 (95% CI 3.1–10.2)
Single-centre, PC, Croatia [48]	258 patients admitted to ICU with sepsis, acute coronary syndrome and acute heart failure with no history of disturbed glucose metabolism or steroid use	Random venous BG in ICU >7.7 mmol/L on at least two occasions	(a) Annual OGTT for 5 years but frequency not specified[a] (b) History; absence of hyperglycaemia before discharge	166	Relative risk 1.97 (95% CI 1.04–3.73)	Relative risk 4.51 (95% CI 1.42–14.30)
Single-centre, PC, Belgium [47]	385 patients aged 18–85 years admitted to a medical-surgical ICU for ≥48 h; patients with pancreatitis, known disturbed glucose metabolism and those using glucose-lowering drugs excluded	Arterial BG >140 mg/dL (>7.8 mmol/L) measured using on-site blood gas analyser	(a) OGTT with or without HbA_{1c} 8 months after ICU admission[a] (b) History; medication review; with or without HbA_{1c}	338	Odds ratio 1.43 (95% CI 0.82–2.50)	Odds ratio 1.95 (95% CI 0.65–5.86)

(continued)

Table 10.3 (continued)

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Multi-centre, RC, Australia [49]	22,473 adult patients surviving ICU admission in Australia; 17,074 without known diabetes	Peak BG within first 24 hours of ICU admission ≥11.1 mmol/L as recorded in national ICU database	(a) Registration with national diabetes register from 30 days up to 8 years after hospital discharge (capture rate 80%); median follow-up 5.3 years (b) Prior record in national diabetes register or record within 30 days of discharge; ICD-10 hospital codes; or peak BG >20 mmol/L	22,473	Not evaluated	Hazard ratio 1.91 (95% CI 1.62–2.26)

SH stress hyperglycaemia, *PC* prospective cohort, *ICU* intensive care unit, *BG* blood glucose, *OGTT* oral glucose tolerance test, *CI* confidence interval, HbA_{1c} glycated haemoglobin, *ICD* International Classification of Diseases

[a]Diabetes was defined according to American Diabetes Association criteria [50]: diabetes – fasting plasma glucose ≥7.0 mmol/L or 2-hour plasma glucose during 75 g OGTT ≥11.1 mmol/L or HbA_{1c} ≥6.5% (48 mmol/mol)

after ICU discharge for prediabetes and diabetes [46, 48]. In the study with the most rigorous follow-up, 582 patients underwent annual oral glucose tolerance tests for 5 years after discharge from the ICU [46]. Patients who experienced stress hyperglycaemia during ICU admission (defined as peak blood glucose >7.7 mmol/L) had a fivefold increased risk of developing diabetes when compared to patients without stress hyperglycaemia. In another study from the same centre, 258 patients admitted to ICU with sepsis, acute coronary syndrome or acute heart failure were also followed up with oral glucose tolerance testing [48]. The risk of incident diabetes was more than four times higher in the stress hyperglycaemia cohort. Whilst the results of these studies are informative, generalisability is limited because of the single-centre study design and the absence of reported illness severity data. In contrast, stress hyperglycaemia (peak blood glucose >7.7 mmol/L) did not identify patients at increased risk of incident diabetes in a similar single-centre study of 385 ICU survivors conducted in Belgium [47]. This contrasting finding may be explained by the comparatively short follow-up period – the primary outcome (development of diabetes) was determined using oral glucose tolerance testing, with or without HbA_{1c} testing, at 8 months after ICU discharge.

The retrospective multi-centre database record linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland (summarised in Table 10.2) included a cohort of 1828 patients who required ICU admission and used a higher threshold to define stress hyperglycaemia than other studies (blood glucose ≥11.1 mmol/L) [22]. Data from the cohort of ICU survivors included in this Scottish study was combined with data from the European single-centre prospective cohort studies [46–48] in a recent meta-analysis [2]. A total of 2923 ICU survivors and 131 cases of incident diabetes were included in the meta-analysis. Stress hyperglycaemia was associated with an increased risk of developing diabetes in survivors of critical illness, with a low-moderate degree of statistical heterogeneity between studies (odds ratio 3.48; 95% confidence interval (CI) 2.02–5.98; I^2 = 36.5%) (Fig. 10.2). Stress hyperglycaemia also identified patients at increased risk of developing prediabetes (defined according to the American Diabetes Association criteria [50]), which is a known risk factor for type 2 diabetes, with an annual conversion rate of 5–10% [51]. A limitation of this meta-analysis was the significant clinical heterogeneity among the included studies.

The largest cohort studied to evaluate whether an association between stress hyperglycaemia and subsequent diabetes exists is a multi-centre retrospective data-linkage cohort of 22,473 patients surviving ICU admission in the state of South Australia [49]. Data that was forwarded to the national (Australian New Zealand Intensive Care Society) ICU database were linked to state-retained hospital-level coding data (matching hospital diagnostic codes for diabetes prior to index hospital discharge), registration with the national diabetes register and the national register of deaths. Stress hyperglycaemia (defined as blood glucose ≥11.1 mmol/L in the first 24 hours of admission) occurred in 17% of patients without diabetes, and the incidence of diabetes following critical illness was almost 5% over a median observation period of 5 years. Stress hyperglycaemia nearly doubled the risk of incident diabetes, and this risk persisted regardless of age or illness severity. This study used the proposed cut-off (blood glucose ≥11.1 mmol/L) at which screening programmes may be beneficial [22]. However, like in several of the previous studies [22, 46, 47], only a single elevated reading was required, which may not be sufficiently specific given that temporary disturbances in blood glucose can occur following use of catecholamines or glucocorticoids in critical illness.

In summary, current evidence suggests that the presence of stress hyperglycaemia during critical illness at least doubles the risk of incident diabetes following hospital discharge.

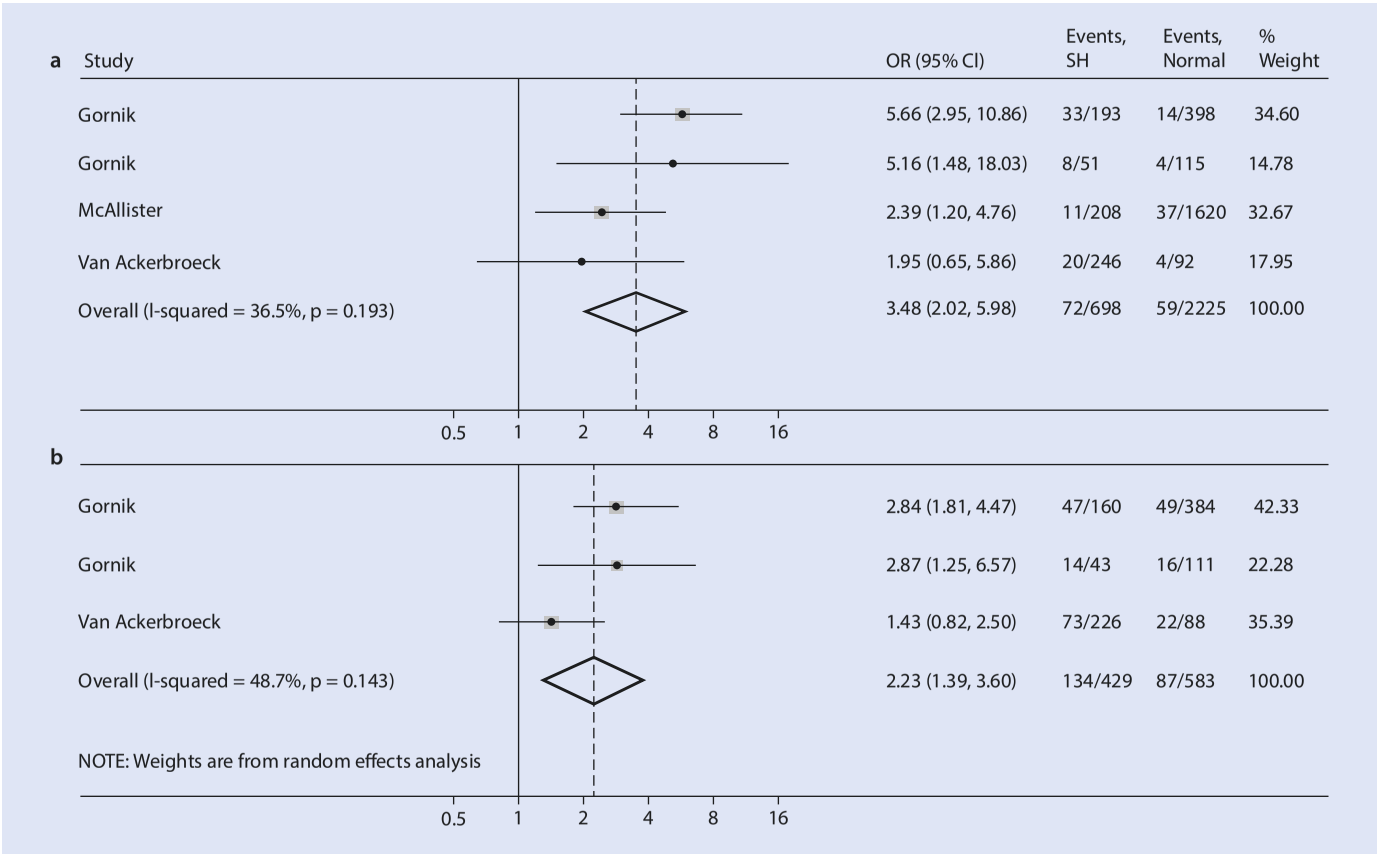


Fig. 10.2 Forest plot showing the risk of **a** incident diabetes and **b** prediabetes in adult ICU patients with stress hyperglycaemia (*Image originally published by BioMed Central* [2]). SH stress hyperglycaemia. Four studies were included in the meta-analysis [22, 46–48]. Prediabetes was defined according to American Diabetes Association criteria [50]: fasting plasma glucose 5.6–6.9 mmol/L (impaired fasting glucose) or 2-hour plasma glucose during 75 g OGTT 7.8–11.0 mmol/L (impaired glucose tolerance) or HbA_{1c} 5.7–6.4% (39–46 mmol/mol)

Accordingly, post-ICU diabetes appears to be a real phenomenon. However, all studies to date have been limited by the use of varying blood glucose thresholds to define stress hyperglycaemia, and blood glucose concentrations have not been reported in relation to nutrient delivery or fasting status. Furthermore, very few studies have measured HbA_{1c} as a way to exclude baseline diabetes, leading to the potential that undiagnosed diabetes may bias estimates of risk.

10.5 Similarities Between the Long-Term Complications of Critical Illness and Those of Diabetes

Many of the complications of critical illness are similar to the known microvascular complications of type 2 diabetes. Nephropathy, autonomic neuropathy and sensorimotor peripheral neuropathy all occur frequently in survivors of critical illness [3–5] and also in patients with type 2 diabetes who have never been critically ill [52]. It is therefore plausible that the development of diabetes after critical illness could exacerbate any underlying long-term complications of critical illness.

Taking nephropathy as an example, critically ill patients who survive an episode of acute kidney injury requiring renal replacement therapy frequently experience poor physical function and mental health even 3 years after hospital discharge [53, 54]. These patients are also at ongoing risk of high mortality and, in those patients still alive at 4 years, albuminuria is present in almost half [55]. Given that albuminuria is a recognised independent risk factor for dialysis requirement, cardiovascular disease and death in cohorts of non-critically ill patients [56, 57] and that albuminuria is a key feature of diabetic nephropathy, it is likely that outcomes will be worse in critically ill patients who subsequently develop diabetes.

Similarly, autonomic dysfunction, which is already prevalent in critical illness and also develops as a complication of type 2 diabetes [58], may be accelerated in at-risk patients and exacerbate symptoms associated with gastroparesis [36] and sexual and bladder dysfunction [59, 60]. Cardiovascular autonomic dysfunction is also strongly associated with mortality both in critically ill cohorts [4] and in patients with type 2 diabetes in the community setting [61] – whether this risk of death is compounded in survivors of critical illness with type 2 diabetes remains unknown.

Finally, the prolonged severe weakness and disability associated with critical illness polyneuropathy [3, 62] may be less likely to recover if post-ICU diabetes develops, given that the known microvascular complications of diabetes include diabetic neuropathy [63, 64].

A significant overlap exists between the long-term complications of critical illness and those of type 2 diabetes, suggesting potential benefits from screening and preventative interventions for prediabetes and type 2 diabetes in survivors at risk of post-ICU diabetes.

10.6 Screening for Post-ICU Diabetes and Potential Preventative Strategies

There is typically an extended time period between the development of type 2 diabetes and its eventual diagnosis, and this delay in clinical diagnosis frequently exacerbates progression of microvascular complications [65]. Therefore, an opportunity exists to explore whether screening programmes in survivors of critical illness who experienced stress

hyperglycaemia can lead to early diagnosis of prediabetes or diabetes and allow intervention to prevent long-term complications. Such a targeted strategy represents a novel approach given that the current evidence base supporting follow-up programmes and interventions for heterogeneous cohorts of ICU survivors is limited [66–69].

It should be recognised that mass general population screening programmes for type 2 diabetes are not always effective [70]. However, targeted screening of groups at high risk, such as women with a history of gestational diabetes, can lead to earlier diagnosis and better health outcomes. In many countries, screening programmes have been instituted during the postpartum period for women with gestational diabetes [20, 71]. Point estimates from meta-analyses suggest that the risk of diabetes following stress hyperglycaemia during critical illness is similar to, or greater than, the risk in women with gestational diabetes over comparable periods of observation [2, 17, 19]. Given the high prevalence of stress hyperglycaemia and that millions of patients are admitted to ICUs worldwide each year, there is potentially a large number of ICU survivors who may benefit from screening and early detection of diabetes or prediabetes. Furthermore, the largest study to date has identified that the risk of incident diabetes following stress hyperglycaemia is greatest in survivors of critical illness aged 50–59 years – a sevenfold increased risk [49]. This is significant because the most cost-effective screening programmes are those which can identify younger populations at risk who have the most potential to benefit from early intervention [72].

The optimal time to screen, duration of screening and best screening test to use (fasting plasma glucose, the 2-hour plasma glucose value during a 75 g oral glucose tolerance test, HbA_{1c} or all of these) for survivors of critical illness are unknown. In critically ill patients with stress hyperglycaemia, HbA_{1c} is reported to be greater than in patients with normal glucose tolerance [47, 73] and, in ambulant populations, HbA_{1c} is a strong predictor of the future risk of diabetes [74]. Repeat HbA_{1c} measurement after ICU discharge to monitor for increments may identify those patients progressing to type 2 diabetes [73] and has the appealing properties of being relatively inexpensive and available at laboratories or primary health-care facilities external to a large hospital that has an ICU, but this has not been studied to date. It is important to note that in other cohorts the benefit of interventions for primary prevention of type 2 diabetes [75, 76] has mainly been demonstrated in patients with impaired glucose tolerance, rather than in individuals with isolated impaired fasting glucose or for those with prediabetes defined by HbA_{1c} criteria. Interventions proven to prevent progression to diabetes in patients diagnosed with prediabetes are however cost-effective and readily available. These interventions include lifestyle modifications such as dietary change, exercise programmes and use of metformin particularly in patients with obesity or prior gestational diabetes [21, 75, 77–80]. None of these interventions have been studied specifically following critical illness.

10.7 Future Directions

There is emerging evidence that stress hyperglycaemia is a risk factor for incident diabetes in survivors of critical illness. To precisely quantify this risk, a multi-centre prospective cohort study with an adequate follow-up period of several years is required. In such a study, it would be important to utilise HbA1c to exclude undiagnosed diabetes at baseline and to define stress hyperglycaemia relative to nutrient delivery and on the basis of repeated blood glucose measurements. In addition, studies which evaluate the mechanisms underlying progressive glucose intolerance following critical illness are needed in

order to guide interventions. Future mechanistic studies could also evaluate autonomic function, insulin and incretin hormone secretion capacity, persistence of insulin resistance (using iso-glycaemic hyperinsulinaemic clamps or sophisticated modelling post oral glucose tolerance testing), persistence of gastric dysmotility, interaction with known risk factors (such as increased body mass index and family history) and physical activity levels post ICU. Finally, it is important to determine whether targeted screening programmes in survivors of critical illness can lead to earlier diagnosis of prediabetes or diabetes and reduce the associated complications that are important to patients.

Conclusion

Stress hyperglycaemia during critical illness is prevalent and appears to identify patients at increased risk of developing diabetes following ICU discharge. The mechanisms underlying post-ICU diabetes remain incompletely understood at present. Further work to determine whether screening and preventative programmes for survivors of critical illness and stress hyperglycaemia are of benefit and cost-effective is required.

Take Home Messages

- Stress hyperglycaemia occurs frequently in the ICU.
- Patients who develop stress hyperglycaemia may be at increased risk of developing type 2 diabetes – current evidence suggests that stress hyperglycaemia may at least double this risk.
- Potential mechanisms implicated in the development of post-ICU diabetes include persistent insulin resistance, autonomic dysfunction, gastric dysmotility, attenuation of the incretin effect, reduced physical activity and individual patient predisposition.
- Post-ICU diabetes can be diagnosed by fasting plasma glucose, an oral glucose tolerance test or HbA1c measurement, using the same diagnostic criteria as type 2 diabetes.
- Patients who experience stress hyperglycaemia during critical illness may benefit from closer follow-up after ICU, but as yet there are no screening programmes or interventions that are proven to be of benefit in this group specifically.

References

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807.
2. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20(1):301.
3. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35.
4. Schmidt H, Hoyer D, Hennen R, Heinroth K, Rauchhaus M, Prondzinsky R, et al. Autonomic dysfunction predicts both 1- and 2-month mortality in middle-aged patients with multiple organ dysfunction syndrome. Crit Care Med. 2008;36(3):967–70.
5. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
6. Nguyen TAN, Ali Abdelhamid Y, Weinel LM, Hatzinikolas S, Kar P, Summers MJ, et al. Postprandial hypotension in older survivors of critical illness. J Crit Care. 2018;45:20–6.
7. Deane AM, Horowitz M. Dysglycaemia in the critically ill – significance and management. Diabetes Obes Metab. 2013;15(9):792–801.

8. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014;40(7):973–80.
9. Kar P, Jones KL, Horowitz M, Deane AM. Management of critically ill patients with type 2 diabetes: the need for personalised therapy. World J Diabetes. 2015;6(5):693–706.
10. Carey LC, Lowery BD, Cloutier CT. Blood sugar and insulin response of humans in shock. Ann Surg. 1970;172(3):342–50.
11. Plummer MP, Deane AM. Dysglycemia and glucose control during sepsis. Clin Chest Med. 2016;37(2):309–19.
12. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36(8):2249–55.
13. Kaukonen KM, Bailey M, Egi M, Orford N, Glassford NJ, Marik PE, et al. Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. Crit Care Med. 2014;42(6):1379–85.
14. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Crit Care Med. 2013;41(6):e93–4.
15. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
16. Smith FG, Sheehy AM, Vincent JL, Coursin DB. Critical illness-induced dysglycaemia: diabetes and beyond. Crit Care. 2010;14(6):327.
17. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773–9.
18. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. J Clin Endocrinol Metab. 2001;86(3):989–93.
19. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with type 2 diabetes. Diabet Med. 2004;21(2):103–13.
20. Kim C, Herman WH, Vijan S. Efficacy and cost of postpartum screening strategies for diabetes among women with histories of gestational diabetes mellitus. Diabetes Care. 2007;30(5):1102–6.
21. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100(4):1646–53.
22. McAllister DA, Hughes KA, Lone N, Mills NL, Sattar N, McKnight J, et al. Stress hyperglycaemia in hospitalised patients and their 3-year risk of diabetes: a Scottish retrospective cohort study. PLoS Med. 2014;11(8):e1001708.
23. Shore S, Borgerding JA, Gylys-Colwell I, McDermott K, Ho PM, Tillquist MN, et al. Association between hyperglycemia at admission during hospitalization for acute myocardial infarction and subsequent diabetes: insights from the veterans administration cardiac care follow-up clinical study. Diabetes Care. 2014;37(2):409–18.
24. MacIntyre EJ, Majumdar SR, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Eurich DT. Stress hyperglycemia and newly diagnosed diabetes in 2124 patients hospitalized with pneumonia. Am J Med. 2012;125(10):1036 e17–23.
25. Gray CS, Scott JF, French JM, Alberti KG, O'Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. Age Ageing. 2004;33(1):71–7.
26. Preiser JC, de Longueville C. Could type 2 diabetes be a component of the post-intensive care syndrome? Crit Care. 2017;21(1):26.
27. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S151–6.
28. Plummer MP, Chapman MJ, Horowitz M, Deane AM. Incretins and the intensivist: what are they and what does an intensivist need to know about them? Crit Care. 2014;18(2):205.
29. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care. 2007;30(2):263–9.
30. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131–57.
31. Nielsen ST, Janum S, Krogh-Madsen R, Solomon TP, Moller K. The incretin effect in critically ill patients: a case-control study. Crit Care. 2015;19:402.

32. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, et al. The effects of critical illness on intestinal glucose sensing, transporters, and absorption. Crit Care Med. 2014;42(1):57–65.
33. Kar P, Cousins CE, Annink CE, Jones KL, Chapman MJ, Meier JJ, et al. Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: a prospective, double blind, randomised, crossover study. Crit Care. 2015;19:20.
34. Deane AM, Chapman MJ, Fraser RJ, Burgstad CM, Besanko LK, Horowitz M. The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: a randomised double-blind placebo-controlled cross over study. Crit Care. 2009;13(3):R67.
35. Pilichiewicz AN, Chaikomin R, Brennan IM, Wishart JM, Rayner CK, Jones KL, et al. Load-dependent effects of duodenal glucose on glycemia, gastrointestinal hormones, antropyloroduodenal motility, and energy intake in healthy men. Am J Physiol Endocrinol Metab. 2007;293(3):E743–53.
36. Kar P, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. Clin Nutr. 2015;34(4):557–64.
37. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015;39(4):441–8.
38. Phillips WT, Schwartz JG, McMahan CA. Rapid gastric emptying in patients with early non-insulin-dependent diabetes mellitus. N Engl J Med. 1991;324(2):130–1.
39. Bertin E, Schneider N, Abdelli N, Wampach H, Cadiot G, Loboguerrero A, et al. Gastric emptying is accelerated in obese type 2 diabetic patients without autonomic neuropathy. Diabetes Metab. 2001;27(3):357–64.
40. Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M. Gastric emptying and glycaemia in health and diabetes mellitus. Nat Rev Endocrinol. 2015;11(2):112–28.
41. Marathe CS, Rayner CK, Bound M, Checklin H, Standfield S, Wishart J, et al. Small intestinal glucose exposure determines the magnitude of the incretin effect in health and type 2 diabetes. Diabetes. 2014;63(8):2668–75.
42. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
43. Schmidt H, Muller-Werdan U, Hoffmann T, Francis DP, Piepoli MF, Rauchhaus M, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. Crit Care Med. 2005;33(9):1994–2002.
44. Cryer PE. Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM. A vicious cycle. Diabetes. 1992;41(3):255–60.
45. Kirwan JP, Solomon TP, Wojta DM, Staten MA, Holloszy JO. Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab. 2009;297(1):E151–6.
46. Gornik I, Vujaklija-Brajkovic A, Renar IP, Gasparovic V. A prospective observational study of the relationship of critical illness associated hyperglycaemia in medical ICU patients and subsequent development of type 2 diabetes. Crit Care. 2010;14(4):R130.
47. Van Ackerbroeck S, Schepens T, Janssens K, Jorens PG, Verbrugghe W, Collet S, et al. Incidence and predisposing factors for the development of disturbed glucose metabolism and DIabetes mellitus AFter Intensive Care admission: the DIAFIC study. Crit Care. 2015;19:355.
48. Gornik I, Vujaklija A, Lukic E, Madzarac G, Gasparovic V. Hyperglycaemia in critical illness is a risk factor for later development of type II diabetes mellitus. Acta Diabetol. 2010;47(Suppl 1):29–33.
49. Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, et al. Stress induced hyperglycemia and the subsequent risk of type 2 diabetes in survivors of critical illness. PLoS One. 2016;11(11):e0165923.
50. American Diabetes A. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(Suppl 1): S13–22.
51. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279–90.
52. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
53. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med. 2005;31(9):1222–8.
54. Korkeila M, Ruokonen E, Takala J. Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med. 2000;26(12):1824–31.

55. Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, et al. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Med. 2014;11(2):e1001601.
56. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation. 2004;110(1):32–5.
57. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331–40.
58. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553–79.
59. Reitz A. Lower urinary tract dysfunction in critical illness polyneuropathy. NeuroRehabilitation. 2013;33(2):329–36.
60. Griffiths J, Gager M, Alder N, Fawcett D, Waldmann C, Quinlan J. A self-report-based study of the incidence and associations of sexual dysfunction in survivors of intensive care treatment. Intensive Care Med. 2006;32(3):445–51.
61. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33(7):1578–84.
62. Koch S, Wollersheim T, Bierbrauer J, Haas K, Morgeli R, Deja M, et al. Long-term recovery in critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve. 2014;50(3):431–6.
63. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
64. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.
65. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care. 1992;15(7):815–9.
66. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41(5):763–75.
67. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
68. Ali Abdelhamid Y, Phillips L, Horowitz M, Deane A. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: study protocol for the SWEET-AS randomised controlled feasibility study. Pilot Feasibility Stud. 2016;2:62.
69. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10.
70. Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care. 2011;34(10):2244–9.
71. Morrison MK, Collins CE, Lowe JM. Postnatal testing for diabetes in Australian women following gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 2009;49(5):494–8.
72. American Diabetes A. Screening for type 2 diabetes. Diabetes Care. 2003;26(Suppl 1):S21–4.
73. Du YT, Kar P, Abdelhamid YA, Horowitz M, Deane AM. Glycated haemoglobin is increased in critically ill patients with stress hyperglycaemia: implications for risk of diabetes in survivors of critical illness. Diabetes Res Clin Pract. 2018;135:73–5.
74. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800–11.
75. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403.
76. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343–50.

77. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371(9626):1783–9.
78. Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006;368(9548):1673–9.
79. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93(12):4774–9.
80. American Diabetes A. 5. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S51–S4.

Suggested Reading

Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807. This review paper provides a comprehensive summary of the pathophysiology and associations of stress hyperglycaemia during critical illness

Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20(1):301. This systematic review and meta-analysis summarises the current literature and evaluates whether stress hyperglycaemia identifies survivors of critical illness at increased risk of developing type 2 diabetes

Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, et al. Stress induced hyperglycemia and the subsequent risk of type 2 diabetes in survivors of critical illness. PLoS One. 2016;11(11):e0165923. This multicentre epidemiological study is the largest to examine the risk of incident type 2 diabetes following stress hyperglycaemia in critical illness. This study was published after the above systematic review

Short- and Long-Term ICU-Acquired Immunosuppression

D. Grimaldi and F. Pène

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_11

Learning Objectives

- Understand that severe inflammatory conditions are associated with an anti-inflammatory response
- To apprehend the ICU patients as immunosuppressed patients
- To describe the main immune alterations after severe injury
- To consider the potential role of immunological alterations in post-discharge complications

11.1 Introduction

Acute severe injuries such as sepsis, trauma, severe hemorrhage, major surgery or cardiac arrest account for most of the ICU admission. Thanks to advances in life support tools and knowledge, to technical progress, a majority of patients now survive the first days of their injury but are then exposed to the development of ICU-acquired infections that are associated with significant morbidity and mortality [1, 2]. The increasing burden of nosocomial infections and the emergence of multidrug resistant bacteria call to urgent progress in preventive treatment of ICU-acquired infections. Although the prolonged use of invasive medical devices and the selection of resistant bacteria remain important determinants of ICU-acquired infections, there is increasing evidence that some acquired immune dysfunctions might contribute to the increased susceptibility to secondary infections despite recovery from the primary insult.

11.2 The Post-injury Acquired Immune Suppression

11.2.1 ICU-Acquired Infections

Preventive bundles associating hygiene compliance and care processes have been shown to be able to reduce catheter-related bloodstream infection (CLABSI) or ventilator-associated pneumonia (VAP). However, if a "0" rate of CLABSI has been demonstrated as an achievable goal, residual incidence rates of ventilator-associated pneumonia have been constantly observed [3], suggesting that additional factors other than hygiene compliance are involved in the susceptibility to VAP. Furthermore, the pattern of VAP-causing pathogens such as *Pseudomonas* spp., *Stenotrophomonas* spp., *Acinetobacter* spp. and *Enterococcus* spp., which are weakly virulent organisms for immunocompetent patients, suggests impaired host immunity in critically ill patients.

More strikingly, opportunistic infections are increasingly recognized in the ICU. Invasive fungal infections are common, mainly invasive candidiasis [4], but also invasive aspergillosis [5] in the absence of overt immunosuppressive conditions such as prolonged neutropenia, AIDS and solid organ transplantation [5].

In addition, critically ill patients frequently exhibit reactivations of *Herpesviridae* cytomegalovirus and herpes simplex viruses [6, 7]. Whether such reactivations are only a marker of immune suppression or also contribute to the immune impairment in critically ill patients remains unclear.

11.2.2 Sepsis-Induced Immune Alterations

Numerous clinical and experimental data suggest that severe critically ill patients exhibit an anti-inflammatory pattern that results in a complex immunosuppression.

Most changes in immune cells induced by acute inflammatory conditions have been first described in septic patients but mostly apply to patients with non-infectious injuries. The immune pathophysiology of sepsis is currently summarized as a sequential inflammatory response rapidly followed by a compensatory anti-inflammatory which may results in complex and sustained immunosuppression affecting both innate and adaptive components of immunity. Quantitative and functional defects in antigen-presenting cells and lymphocytes account for profound alterations in the immune synapse and therefore in the priming and orientation of the immune response towards superimposed pathogens. It is noteworthy that immune dysfunctions in patients have been mainly addressed in circulating immune cells, albeit consistent with those observed in tissue-resident immune cells obtained from human autopsic studies or experimental animal models [8, 9]. Most immune dysfunctions have been associated with relevant outcomes such as mortality and development of ICU-acquired infections.

11.2.2.1 Monocyte Deactivation

Monocytes are abundant circulating precursors of tissue macrophages. Sepsis induces functional changes resulting in a phenotype called "monocyte deactivation" on the basis of decreased membrane expression of the antigen presentation complex HLA-DR and its co-activation molecule such as CD86 and increased expression of inhibitory co-stimulation molecules such as PDL-1 [10, 11]. As of today, the membrane expression of HLA-DR as measured by flow cytometry represents the most reliable biomarker of sepsis-induced immunosuppression. The persistent decrease of HLA-DR has been associated with increased mortality, and it has been identified as an independent risk factor of ICU-acquired infections when adjusted with common clinical confounders such as the initial severity of patients and the use of invasive procedures [12, 13]. These changes in the antigen presentation apparel are associated with impaired pro-inflammatory cytokines secretion in response to an *ex vivo* LPS challenge (reviewed in [14]).

11.2.2.2 Alterations in Dendritic Cells

Dendritic cells (DCs) constitute a pivotal link between innate and adaptive response and play a critical role in the integration of the inflammatory response. As "professional" antigen-presenting cells, they initiate and polarize the adaptive immune response in activating T cells. Massive apoptosis of DCs in secondary lymphoid organs has been reported in patients who died from sepsis [10, 15]. DCs account for a very small proportion of circulating leukocytes, improvements in flow cytometry has allowed addressing circulating DC subsets in patients. Septic shock has been associated with DCs depletion and down-regulation of HLA-DR membrane expression [16, 17]. Furthermore, persistent depletion of DCs has been associated with the further development of ICU-acquired infections [17].

11.2.2.3 Lymphocyte Apoptosis

Lymphocyte apoptosis is a hallmark of sepsis. The pioneering autopsic study by Hotchkiss and colleagues highlighted extensive B- and T-cell apoptosis in spleens from patients deceased from sepsis [18]. It is commonly reflected by lymphopaenia in critically ill patients, which is associated with the severity of the disease [19]. However, persistent lymphopaenia has not been constantly linked to an increased susceptibility to ICU-acquired infections [20, 21]. It is noteworthy that the proportion of immunosuppressive T-regulatory subsets is increased in sepsis, as a result of relative preservation from apoptosis and expansion under the influence of tolerogenic DCs [22, 23]. The relative increase

of Tregs contributes to lymphocyte anergy in human [13, 16, 24] and was associated with a susceptibility to superinfections in the largest multicentric prospective study ever performed in the field [13].

11.2.2.4 Myeloid-derived Suppressor Cells

The identification of an innate cells subset called myeloid-derived suppressor cells (MDSCs) has provided new insights into the regulation of sepsis-induced immunosuppression. MDSCs are immature myeloid cells distributed in two granulocytic and monocytic subsets and carry potent immunosuppressive properties through repression of T-cell functions or expansion of Tregs [25]. MDSCs undergo expansion under various chronic and acute inflammatory conditions. In patients with sepsis, two studies reported an increase of circulating MDSCs that was associated (mostly for granulocytic MDSC) with an increase in ICU-acquired infections [26, 27].

11.2.2.5 Alterations in the Immunological Synapse

The crosstalk between innate immunity and adaptive immunity occurs through a tight interaction between antigen-presenting cells (APC) such as monocytes/macrophages, dendritic cells and $CD4^+$ T-helper lymphocyte. Both cells interact in forming a so-called immune synapse through direct molecule-molecule interactions and cytokine-mediated paracrine effects. The type and amplitude of the resulting immune response relies on the nature of the signals delivered by APC to lymphocytes. Sepsis induces profound functional alterations in the immune synapse through decreased expression of the antigen presentation apparel and its co-stimulatory molecules (CD86, CD40), whereas co-inhibitory checkpoint signals (PD-L1, PD-L2, PD1, CTLA-4) are increased, including preferential production of the prototypic anti-inflammatory cytokine IL-10. Signal alterations within the immune synapse prevent the development of a potent Th1 or Th17 immune response against pathogens encountered in critically ill patients and rather promote an aberrant anergic or immunosuppressive response.

11.2.3 A Broader Concept of Post-injury Immune Dysfunction

Although we focused in this chapter on post-septic immune dysfunction, a body of evidences supports the concept of post-aggressive immunopathy following acute severe inflammatory disorders. Indeed, the leucocyte transcriptional responses to trauma, burn or sepsis appear quite similar [28], and there is now evidence that extensive tissue damage induced by trauma, major surgery, burn or even cerebral haemorrhage may also impact on the immune system in a similar manner as severe infections [29]. The main immune dysfunctions during sterile injuries are depicted in Table 11.1. In general, immune alterations appear more pronounced in septic shock than in non-infectious disorders with similar extent of organ failures [17, 30]. The time from insult to ICU admission, short and often clearly defined in trauma or burn while most often unclear in sepsis, may account for differences between severe infections and non-infectious disorders. Of note, immune dysfunctions induced by non-infectious disorders may also favour the development of secondary infections promoting persistent immune alterations as described above. Finally, critically ill patients are exposed to several treatments and procedures including mechanical ventilation, red blood cell transfusions, stress-dose corticosteroids, extracorporeal circulation or sedatives that exhibit local or systemic immunomodulatory properties.

Table 11.1 Different post-aggressive immune dysfunctions subsets and their association with mortality and/or ICU-acquired infections

Immune dysfunctions	Association with mortality after sepsis	Association with ICU-acquired infections after sepsis	Demonstrated in sterile acute injuries	Main References[a]
Monocyte deactivation HLA-DR expression decrease	Association reported in multiple studies	Independent association after adjustment and competitive risk analyses	Trauma Cerebral hemorrhage Cardiac arrest Major surgery Burn	[12, 13, 30, 60–65]
Depletion of dendritic cells	Association reported in one study	Association in some studies	Cerebral hemorrhage Cardiac arrest Burn	[16, 17, 29, 66, 67]
Expansion of myeloid suppressor cells	Association reported in some studies	Time dependent association reported in some studies	No	[20, 21]
Lymphopenia	Association reported in multiple studies	Conflicting results	Trauma Major surgery Cardiac arrest Burns	[13, 19–21, 68]
Increase in Tregs	Association reported in two studies	Association reported in one study	Trauma Burn	[13, 23, 24, 69–71]
Overexpression of inhibitory molecules (PD-1, PD-L1, CTLA-4, BTLA)	Association reported in some studies	Association reported in some studies	Conflicting results	[10, 11, 72–74]

BTLA B- and T-lymphocyte attenuator, *CTLA* cytotoxic T-lymphocyte-associated antigen 4, *HLA* human leucocytes antigen, *PD-1* program cell death-1, *PD-L1* program cell death ligand 1, *Tregs* regulatory T-cells
[a]References are not exhaustive

11.3 Immuno-Inflammatory Sequelae in ICU Survivors

11.3.1 Post-discharge Infectious and Non-infectious Complications

The improvements in intensive care and organ failure support have dramatically improved the short-term survival to critical illnesses and resulted in an emerging morbidity related to new patterns of frailty [31]. The inability to recover from acute life-threatening conditions resulting in dependence to advanced medical care and organ failure and often requiring prolonged ICU stay defines a new clinical picture of chronic critical illness [32].

Furthermore, it has now become clear that the burden of acute life-threatening conditions extends beyond the acute phase of intensive care and hospitalization. This has been largely emphasized for sepsis survivors who appear particularly vulnerable to long-term sepsis recurrence, as well as non-infectious complications.

The pioneer report by Quartin and colleagues in 1997 highlighted the higher risk of death in severe sepsis and septic shock patients following hospital discharge [33]. Since then, multiple studies confirmed that sepsis survivors with or without associated chronic comorbidities exhibit a worse long-term prognosis than nonseptic counterparts. Thus, the 10-year mortality was higher in previously healthy patients who survived severe sepsis and septic shock, as compared to patients who survived nonseptic critical illness and to the general population in the same age range [34]. Prescott addressed the respective contributions of sepsis and pre-existing comorbid conditions on long-term mortality and identified that sepsis was associated with a 22% increase in 2-year death that could not be explained by the underlying health status [35]. Part of the vulnerability of sepsis survivors might be related to a sustained susceptibility towards subsequent infections, after the common short-term efficacy endpoints have been reached (28-day, ICU and hospital survival). Survivors of sepsis displayed a higher incidence of subsequent infectious complications, early within the first 3 months or later on, up to 1 year as compared to patients who survived nonseptic critical illness and to the general age-matched population [36–38]. Similarly to critically ill patients in the ICU, post-septic patients appear particularly vulnerable to pneumonia and infections caused by opportunistic bacterial pathogens as a result of defective immunity [38].

Besides an increased susceptibility to infections, some studies also reported that severe infections may favour the development of non-infectious complications such as cancer and cardiovascular diseases. Thus, critically ill patients are prone to cardiovascular complications in the early phase of management, related to impaired regional circulations, acute inflammatory conditions, anaemia, increased cardiac workload and microcirculatory alterations. Furthermore, sepsis seems to induce a long-term susceptibility to cardiovascular complications, far beyond the early phase of management and hospital discharge [39, 40]. In the same way, some reports suggested that a history of bacterial infection and/or the recurrent use of antibiotics were associated with an increased risk of development of new-onset hematological and solid malignancies [41–44]. In cancer patients undergoing major elective surgery, postoperative sepsis was associated with increased 4-year mortality suggesting an impact of sepsis episodes on the subsequent oncological prognosis [45].

11.3.2 Baseline and Acquired Determinants of Post-discharge Complications

Several mechanisms driving the long-term susceptibility to sepsis recurrence have been proposed (Fig. 11.1). The major reason obviously lies in the impaired baseline health status of most septic patients, in relation with ageing, functional disability and chronic immune and non-immune comorbid conditions. It appears not only as a major determinant of susceptibility to and severity of sepsis but also constitutes a major hurdle to further recovery from acute critical illness. Indeed, sepsis survivors exhibit a high incidence of sequelae as well as physical and cognitive impairment resulting in prolonged immobilization, denutrition and sustained requirements for advanced supportive care such as vascular or urinary catheters, artificial nutrition and care of chronic wounds.

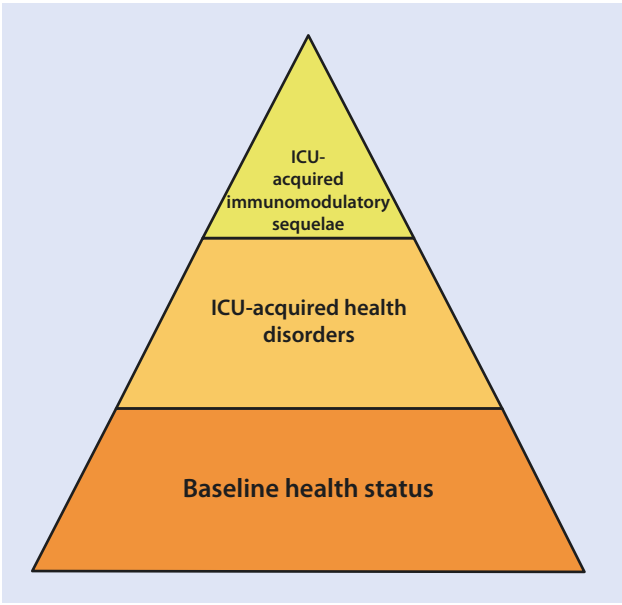


Fig. 11.1 Contributions of baseline and ICU-acquired health disorders in the susceptibility to long-term complications in ICU survivors. The baseline health status, including ageing, excessive alcohol intake, smoking, disability, denutrition, diabetes, cancer, immunosuppression, chronic organ dysfunctions and presence of long-term implanted devices, accounts for an absolute risk of infectious and non-infectious complications. ICU-acquired health disorders, including prolonged immobilization, swallowing difficulty, denutrition, maintenance of intravascular and urinary catheters, chronic wounds and new-onset or worsened chronic organ dysfunctions, add to the risk of delayed complications. The roles of ICU-acquired immunomodulatory sequelae, including sustained immune cell dysfunctions, accelerated atherosclerosis as well as microbiome disruption, remain questionable

Clinical data and animal models have provided a bunch of evidence linking sepsis-induced immune dysfunctions with an increased susceptibility to short-term secondary infections. However, whether early or sustained immune and inflammatory alterations may drive the post-discharge development of both infectious and non-infectious complications in sepsis survivors is still largely unexplored. A substudy using the MARS cohort of severe sepsis and septic shock reported an association between elevated IL-6 levels measured at the time of ICU discharge and 1-year mortality. This association remained significant after adjustment with the site of infection and with variables representative of patients' underlying health status (age, Charlson comorbidity index, immunodeficiency) [46]. Another study reported serial measurements of 15 plasma biomarkers in 55 abdominal sepsis survivors. At the time of ICU discharge, higher levels of the cell damage marker HMGB1 and lower levels of the pro-resolving lipid mediator resolvin D5 (RvD5) were both associated with increased 1-year mortality, though not adjusted with underlying health status. Measurements at 1 year were suggestive of incomplete restoration of hemostasis, of still undetermined significance [47].

Very few studies have investigated whether the hallmark immune dysfunctions induced by sepsis may be sustained beyond ICU and hospital discharge. Zorio and colleagues assessed the persistence of monocyte deactivation and lymphopaenia in septic shock survivors at the time of ICU discharge and at 6 months [48]. Whereas decreased

HLA-DR expression or lymphopaenia was still present at the time of ICU discharge, more delayed assessment showed that lymphocyte counts and distribution as well as HLA-DR expression onto monocytes surface were restored at 6 months. Shalova and colleagues addressed the transcriptomic profile of monocytes obtained from septic patients at the time of ICU admission as well as 1–3 month after resolution. The transcriptomic profile of LPS-stimulated recovery monocytes was very similar to the baseline profile of monocytes obtained from healthy controls, suggesting that the sepsis-induced functional alterations in monocytes are rapidly resolving in the absence of superimposed insults [49]. These results suggest that the main immune alterations classically associated with the development of ICU-acquired infections are not sustained over time and as such are unlikely to explain the eventual increased susceptibility to infections. However, it is noteworthy that these studies have been performed in selected patients free of prior immune comorbidities and therefore with preserved potential of immune recovery. Whether ICU-acquired immune dysfunctions may worsen the immune status of previously immunocompromised patients and thereby add to risk of short-term or long-term susceptibility to infections has been specifically addressed yet.

Some alternative mechanisms of susceptibility to sepsis recurrence are emerging from the microbiome revolution in the pathophysiology of diseases. Microbiome disruption is already known to promote infections caused by *Clostridium difficile* but may also favor infections by alternative pathogens arising from the digestive tract. Prescott and colleagues reported that the risk of subsequent sepsis was 30% higher in patients with prior infection-related hospitalizations than in patients discharged from non-infection-related hospitalizations. The risk was 70% higher for patients previously treated for *Clostridium difficile* infections as a consequence of major microbiome disruption [50]. In the same way, a large observational study of more than 14 million hospital stays reported a 65% increase in the risk of subsequent sepsis within 90 days post-discharge in patients previously exposed to high-risk antibiotics or increased quantities of antibiotics, both likely to have some dramatic impact on dysbiosis [51].

As mentioned above, sepsis survivors also display increased susceptibility towards non-infectious complications. It is likely that the underlying baseline health status and lifestyle may largely account for the particular vulnerability of sepsis survivors towards cardiovascular diseases or cancer. In addition, multiple factors, including increased cardiac workload, chronic anemia, procoagulant hemostatic balance and interruption of maintenance treatment such as antiplatelet agents, may favor new-onset or recurrent cardiovascular events in the setting of sepsis during the acute and recovery phases. In patients with severe community-acquired pneumonia, the persistence of high IL-6 and IL-10 levels at the time of hospital discharge was associated with an increased risk of death at 1 year caused by cardiovascular diseases and cancer [52]. Using an experimental model of polymicrobial sepsis, post-septic mice demonstrated accelerated atherosclerosis progression [53]. Besides impaired immunity to infections, it has been postulated that bacterial sepsis may also alter anticancer immunosurveillance. Accordingly, experimental models reported that post-septic animals exhibited accelerated malignant tumor growth, in relation with the systemic and intra-tumoral expansion of immunosuppressive cells such as regulatory T-cells or myeloid-derived suppressor cells, or the accumulation of tumor-promoting macrophages [54–56]. Recent data also suggest that microbiome disruption induced by antimicrobials may impact on epithelial carcinogenesis and antitumoral immunosurveillance [57, 58].

11.4 Perspectives

Severe acute inflammatory conditions, in particular severe infections, are associated with a complex immune dysfunction associated with increased risk of ICU-acquired infections. Decades of interventional trials aimed to modulate the early pro-inflammatory response in sepsis failed to improve outcome. The burden of ICU-acquired infections and the advances in the comprehension of sepsis-induced immune dysfunctions provided a strong rationale for attempting to reverse immune dysfunctions in septic patients. Some therapeutic approaches to reverse monocyte deactivation (IFN-γ, GM-CSF), to sustain the proliferation and survival of lymphocytes (IL-7) and to restore activating signals in the immune synapse (PD1/PD-L1 antibodies) are currently under clinical evaluation [59].

The emerging concept of "post-ICU syndrome" sheds a light on major health issues in ICU survivors, long after hospital discharge and apparent recovery from the acute insult. Whether long-term complications are related to individual predisposition, underlying comorbidities or to the acute condition should now be investigated, as well as the associated risk stratification. This is the first step to propose individualized long-term follow-up and eventually specific preventive interventions in order to prevent and/or early detect delayed complications in ICU survivors.

Take Home Messages

- Sepsis and other acute inflammatory disorders induce quantitative and functional immune dysfunctions.
- ICU-acquired immunosuppression is associated with increased susceptibility to nosocomial infections.
- Sepsis survivors are prone to long-term infectious and non-infectious complications.

References

1. Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, et al. Timing and causes of death in septic shock. Ann Intensive Care. [Internet]. 2015 [cited 2018 Jun 25];5(1). Available from: http://www.annalsofintensivecare.com/content/5/1/16
2. Otto GP, Sossdorf M, Claus RA, Rödel J, Menge K, Reinhart K, et al. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Crit Care. 2011;15(4):R183.
3. Bouadma L, Deslandes E, Lolom I, Le Corre B, Mourvillier B, Regnier B, et al. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. Clin Infect Dis. 2010;51(10):1115–22.
4. Tortorano AM, Dho G, Prigitano A, Breda G, Grancini A, Emmi V, et al. Invasive fungal infections in the intensive care unit: a multicentre, prospective, observational study in Italy (2006–2008): fungal infections in intensive care unit. Mycoses. 2012;55(1):73–9.
5. Taccone F, Van den Abeele A-M, Bulpa P, Misset B, Meersseman W, Cardoso T, et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care. 2015;19(1):7.
6. Limaye AP, Kirby KA, Rubenfeld GD, Leisenring WM, Bulger EM, Neff MJ, Gibran NS, Huang ML, Santo Hayes TK, Corey L, Boeckh M. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA. 2008;300(4):413.
7. Luyt C-E, Combes A, Deback C, Aubriot-Lorton M-H, Nieszkowska A, Trouillet J-L, et al. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. Am J Respir Crit Care Med. 2007;175(9):935–42.

8. Pène F, Ait-Oufella H, Taccone FS, Monneret G, Sharshar T, Tamion F, et al. Insights and limits of translational research in critical care medicine. Ann Intensive Care. [Internet]. 2015 [cited 2018 Jun 25];5(1). Available from: http://www.annalsofintensivecare.com/content/5/1/8
9. Grimaldi D, Llitjos JF, Pène F. Post-infectious immune suppression: a new paradigm of severe infections. Médecine Mal Infect. 2014;44(10):455–63.
10. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA. 2011;306(23):2594.
11. Guignant C, Lepape A, Huang X, Kherouf H, Denis L, Poitevin F, et al. Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients. Crit Care. 2011;15(2):R99.
12. Landelle C, Lepape A, Voirin N, Tognet E, Venet F, Bohé J, et al. Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock. Intensive Care Med. 2010;36(11):1859–66.
13. Conway Morris A, Datta D, Shankar-Hari M, Stephen J, Weir CJ, Rennie J, et al. Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. Intensive Care Med. 2018;44(5):627–35.
14. Cavaillon J-M, Adib-Conquy M. Monocytes/macrophages and sepsis. Crit Care Med. 2005;33(12 Suppl):S506–9.
15. Hotchkiss RS, Tinsley KW, Swanson PE, Grayson MH, Osborne DF, Wagner TH, et al. Depletion of dendritic cells, but not macrophages, in patients with sepsis. J Immunol Baltim Md 1950. 2002;168(5):2493–500.
16. Guisset O, Dilhuydy M-S, Thiébaut R, Lefèvre J, Camou F, Sarrat A, et al. Decrease in circulating dendritic cells predicts fatal outcome in septic shock. Intensive Care Med. 2007;33(1):148–52.
17. Grimaldi D, Louis S, Pène F, Sirgo G, Rousseau C, Claessens YE, et al. Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock. Intensive Care Med. 2011;37(9):1438–46.
18. Hotchkiss RS, Tinsley KW, Swanson PE, Schmieg RE, Hui JJ, Chang KC, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. J Immunol Baltim Md 1950. 2001;166(11):6952–63.
19. Girardot T, Rimmelé T, Venet F, Monneret G. Apoptosis-induced lymphopenia in sepsis and other severe injuries. Apoptosis. 2017;22(2):295–305.
20. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. Shock. 2014;42(5):383–91.
21. Grimaldi D, Le Bourhis L, Sauneuf B, Dechartres A, Rousseau C, Ouaaz F, et al. Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. Intensive Care Med. 2014;40(2):192–201.
22. Kushwah R, Hu J. Role of dendritic cells in the induction of regulatory T cells. Cell Biosci. 2011;1(1):20.
23. Venet F, Pachot A, Debard A-L, Bohé J, Bienvenu J, Lepape A, et al. Increased percentage of CD4+CD25+ regulatory T cells during septic shock is due to the decrease of CD4+CD25- lymphocytes. Crit Care Med. 2004;32(11):2329–31.
24. Venet F, Chung C-S, Kherouf H, Geeraert A, Malcus C, Poitevin F, et al. Increased circulating regulatory T cells (CD4+CD25+CD127−) contribute to lymphocyte anergy in septic shock patients. Intensive Care Med. 2009;35(4):678–86.
25. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. Nat Immunol. 2018;19(2):108–19.
26. Uhel F, Azzaoui I, Grégoire M, Pangault C, Dulong J, Tadié J-M, et al. Early expansion of circulating granulocytic myeloid-derived suppressor cells predicts development of nosocomial infections in patients with sepsis. Am J Respir Crit Care Med. 2017;196(3):315–27.
27. Mathias B, Delmas AL, Ozrazgat-Baslanti T, Vanzant EL, Szpila BE, Mohr AM, et al. Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg. 2017;265(4):827–34.
28. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci. 2013;110(9):3507–12.
29. Asehnoune K, Roquilly A, Abraham E. Innate immune dysfunction in trauma patients: from pathophysiology to treatment. Anesthesiology. 2012;117(2):411–6.
30. Lukaszewicz A-C, Grienay M, Resche-Rigon M, Pirracchio R, Faivre V, Boval B, et al. Monocytic HLA-DR expression in intensive care patients: interest for prognosis and secondary infection prediction∗. Crit Care Med. 2009;37(10):2746–52.

31. Prescott HC, Angus DC. Enhancing recovery from Sepsis: a review. JAMA. 2018;319(1):62.
32. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, et al. The epidemiology of chronic critical illness in the United States*. Crit Care Med. 2015;43(2):282–7.
33. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. JAMA. 1997; 277(13):1058–63.
34. Linder A, Guh D, Boyd JH, Walley KR, Anis AH, Russell JA. Long-term (10-year) mortality of younger previously healthy patients with severe sepsis/septic shock is worse than that of patients with non-septic critical illness and of the general population. Crit Care Med. 2014;42(10):2211–8.
35. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. BMJ. 2016;353:i2375.
36. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. JAMA. 2015;313(10):1055.
37. Shen H-N, Lu C-L, Yang H-H. Risk of recurrence after surviving severe sepsis: a matched Cohort study. Crit Care Med. 2016;44(10):1833–41.
38. Wang T, Derhovanessian A, De Cruz S, Belperio JA, Deng JC, Hoo GS. Subsequent infections in survivors of Sepsis: epidemiology and outcomes. J Intensive Care Med. 2014;29(2):87–95.
39. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. Am J Respir Crit Care Med. 2014;189(9):1065–74.
40. Ou S-M, Chu H, Chao P-W, Lee Y-J, Kuo S-C, Chen T-J, et al. Long-term mortality and major adverse cardiovascular events in sepsis survivors. A Nationwide population-based study. Am J Respir Crit Care Med. 2016;194(2):209–17.
41. Titmarsh GJ, McMullin MF, McShane CM, Clarke M, Engels EA, Anderson LA. Community-acquired infections and their association with myeloid malignancies. Cancer Epidemiol. 2014;38(1):56–61.
42. Kristinsson SY, Björkholm M, Hultcrantz M, Derolf ÅR, Landgren O, Goldin LR. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. J Clin Oncol. 2011;29(21):2897–903.
43. Boursi B, Mamtani R, Haynes K, Yang Y-X. Recurrent antibiotic exposure may promote cancer formation – another step in understanding the role of the human microbiota? Eur J Cancer. 2015;51(17):2655–64.
44. Liu Z, Mahale P, Engels EA. Sepsis and risk of cancer among elderly adults in the United States. Clin Infect Dis. [Internet]. 2018 [cited 2018 Sep 12]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciy530/5049133
45. Mokart D, Giaoui E, Barbier L, Lambert J, Sannini A, Chow-Chine L, et al. Postoperative sepsis in cancer patients undergoing major elective digestive surgery is associated with increased long-term mortality. J Crit Care. 2016;31(1):48–53.
46. Frencken JF, van Vught LA, Peelen LM, Ong DSY, Klein Klouwenberg PMC, Horn J, et al. An unbalanced inflammatory cytokine response is not associated with mortality following sepsis: a prospective cohort study. Crit Care Med. 2017;45(5):e493–9.
47. Riché F, Chousterman BG, Valleur P, Mebazaa A, Launay J-M, Gayat E. Protracted immune disorders at one year after ICU discharge in patients with septic shock. Crit Care. [Internet]. 2018 [cited 2018 Aug 23];22(1). Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1934-4
48. Zorio V, Venet F, Delwarde B, Floccard B, Marcotte G, Textoris J, et al. Assessment of sepsis-induced immunosuppression at ICU discharge and 6 months after ICU discharge. Ann Intensive Care. [Internet]. 2017 [cited 2018 Aug 23];7(1). Available from: http://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-017-0304-3
49. Shalova IN, Lim JY, Chittezhath M, Zinkernagel AS, Beasley F, Hernández-Jiménez E, et al. Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1α. Immunity. 2015;42(3):484–98.
50. Prescott HC, Dickson RP, Rogers MAM, Langa KM, Iwashyna TJ. Hospitalization type and subsequent severe sepsis. Am J Respir Crit Care Med. 2015;192(5):581–8.
51. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. Clin Infect Dis. 2018;66(7): 1004–12.
52. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. Am J Respir Crit Care Med. 2008;177(11):1242–7.

53. Kaynar AM, Yende S, Zhu L, Frederick DR, Chambers R, Burton CL, et al. Effects of intra-abdominal sepsis on atherosclerosis in mice. Crit Care [Internet]. 2014 [cited 2018 Aug 23];18(5). Available from: http://ccforum.biomedcentral.com/articles/10.1186/s13054-014-0469-1.
54. Cavassani KA, Carson WF, Moreira AP, Wen H, Schaller MA, Ishii M, et al. The post sepsis-induced expansion and enhanced function of regulatory T cells create an environment to potentiate tumor growth. Blood. 2010;115(22):4403–11.
55. Mota JM, Leite CA, Souza LE, Melo PH, Nascimento DC, de-Deus-Wagatsuma VM, et al. Post-sepsis state induces tumor-associated macrophage accumulation through CXCR4/CXCL12 and favors tumor progression in mice. Cancer Immunol Res. 2016;4(4):312–22.
56. Llitjos J-F, Auffray C, Alby-Laurent F, Rousseau C, Merdji H, Bonilla N, et al. Sepsis-induced expansion of granulocytic myeloid-derived suppressor cells promotes tumour growth through toll-like receptor 4: sepsis-induced MDSC and tumour growth. J Pathol. 2016;239(4):473–83.
57. Routy B, Gopalakrishnan V, Daillère R, Zitvogel L, Wargo JA, Kroemer G. The gut microbiota influences anticancer immunosurveillance and general health. Nat Rev Clin Oncol. 2018;15(6):382–96.
58. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science. 2018;359(6371):91–7.
59. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13(3):260–8.
60. Monneret G, Lepape A, Voirin N, Bohé J, Venet F, Debard A-L, et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock. Intensive Care Med. 2006;32(8):1175–83.
61. Döcke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. Nat Med. 1997;3(6):678–81.
62. Sarrafzadeh A, Schlenk F, Meisel A, Dreier J, Vajkoczy P, Meisel C. Immunodepression after aneurysmal subarachnoid hemorrhage. Stroke. 2011;42(1):53–8.
63. Venet F, Cour M, Demaret J, Monneret G, Argaud L. Decreased monocyte HLA-DR expression in patients after non-shockable out-of-hospital cardiac arrest. Shock. 2016;46(1):33–6.
64. Yang H, Yu Y, Chai J, Hu S, Sheng Z, Yao Y. Low HLA-DR expression on CD14+ monocytes of burn victims with sepsis, and the effect of carbachol in vitro. Burns. 2008;34(8):1158–62.
65. Galbraith N, Walker S, Galandiuk S, Gardner S, Polk HC. The significance and challenges of monocyte impairment: for the ill patient and the surgeon. Surg Infect. 2016;17(3):303–12.
66. Poehlmann H, Schefold JC, Zuckermann-Becker H, Volk H-D, Meisel C. Phenotype changes and impaired function of dendritic cell subsets in patients with sepsis: a prospective observational analysis. Crit Care. 2009;13(4):R119.
67. D'Arpa N, Accardo-Palumbo A, Amato G, D'Amelio L, Pileri D, Cataldo V, et al. Circulating dendritic cells following burn. Burns. 2009;35(4):513–8.
68. Villois P, Grimaldi D, Spadaro S, Shinotsuka CR, Fontana V, Scolletta S, et al. Lymphopaenia in cardiac arrest patients. Ann Intensive Care [Internet]. 2017;7:85. [cited 2018 Aug 22];7(1). Available from: http://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-017-0308-z
69. Leng F-Y, Liu J-L, Liu Z-J, Yin J-Y, Qu H-P. Increased proportion of CD4+CD25+Foxp3+ regulatory T cells during early-stage sepsis in ICU patients. J Microbiol Immunol Infect. 2013;46(5):338–44.
70. MacConmara MP, Maung AA, Fujimi S, McKenna AM, Delisle A, Lapchak PH, et al. Increased CD4+ CD25+ T regulatory cell activity in trauma patients depresses protective Th1 immunity. Ann Surg. 2006;244(4):514–23.
71. Huang L, Yao Y, Dong N, Yu Y, He L, Sheng Z. Association between regulatory T cell activity and sepsis and outcome of severely burned patients: a prospective, observational study. Crit Care. 2010;14(1):R3.
72. Chang K, Svabek C, Vazquez-Guillamet C, Sato B, Rasche D, Wilson S, et al. Targeting the programmed cell death 1: programmed cell death ligand 1 pathway reverses T cell exhaustion in patients with sepsis. Crit Care. 2014;18(1):R3.
73. Shubin NJ, Monaghan SF, Heffernan DS, Chung C-S, Ayala A. B and T lymphocyte attenuator expression on CD4+ T-cells associates with sepsis and subsequent infections in ICU patients. Crit Care. 2013;17(6):R276.
74. Lange A, Sundén-Cullberg J, Magnuson A, Hultgren O. Soluble B and T lymphocyte attenuator correlates to disease severity in Sepsis and high levels are associated with an increased risk of mortality. PLoS One. 2017;12(1):e0169176, Bouchama A, editor

Cognitive/ Psychological Impairment

Contents

PTSD After Critical Illness: Current Issues and Future Directions

James C. Jackson, Caroline Lassen-Greene, Jennifer E. Jutte, and Kristina Stepanovic

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_12

Learning Objectives

- After reading the chapter, individuals will be able to:
- Describe clinical features of PTSD in survivors of critical illness.
- Articulate key risk factors that underlie PTSD.
- Explain the concept of post-traumatic growth.
- Recognize common expressions of PTSD following critical illness.

12.1 Introduction

For millennia, sages of various kinds have recognized that a phenomenon exists in which individuals experience emotional distress following exposure to trauma [1]. Our understanding of what is now known as post-traumatic stress disorder (PTSD) has long revolved around survivors of war, and, indeed, references to the impact of combat on aspects of human functioning are replete in ancient and more contemporary literature, predating the development of the modern *Diagnostic and Statistical Manual* (DSM) [1]. In previous times, terms like "shell shock" and "battle fatigue" anchored the nascent concept of PTSD squarely in the warfare-related domain and popular understandings of PTSD continue to focus – not incorrectly, but incompletely – on certain populations to the exclusion of others. We now understand that critical illness and many other medical concerns are traumatic in their own right. In North America alone, nearly six million people experience critical illness annually [2]. These individuals, not surprisingly, often develop PTSD [3]. By way of review, PTSD is a syndrome that involves the existence of symptoms across a range of dimensions including intrusion, avoidance, negative changes in cognition or mood, and arousal/avoidance. These symptoms must be present for at least 1 month and they must contribute to some degree of meaningful clinical impairment (▶ Box 12.1).

Box 12.1: PTSD Diagnostic Criteria – DSM V PTSD Diagnostic Criteria – DSM V

Criterion A: Exposure to a traumatic stressor

Criterion B: Presence of intrusive symptoms such as unwanted memories, flashbacks, and distress after exposure to reminders of trauma

Criterion C: Presence of avoidant symptoms such as avoidance of trauma-related thoughts and feelings or external reminders

Criterion D: Presence of negative alterations in cognition and mood such as marked feelings of isolation or the sense that one's environment is overwhelmingly dangerous

Criterion E: Presence of symptoms of arousal or reactivity such as irritability, hypervigilance, or sleeping problems

To qualify for a diagnosis of PTSD, individuals must meet Criterion A; have at least one symptom in B, C, and E; and have at least two symptoms in D.

Symptoms must be present for at least a month, must impact functioning in a negative way, and must not be better explained by other factors such as medication or substance abuse.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC

12.2 Risk Factors for PTSD in ICU Survivors

While critical illness is consistently traumatizing, a consistent question related to PTSD pertains to why it is that two individuals with the same exposure often have wildly different experiences. For example, what explains the fact that one individual with a brief episode of sepsis with a short hospital stay and no mechanical ventilation is profoundly traumatized, while an individual with a 3-month-long critical illness marked by multiple surgeries has virtually no symptoms of PTSD at all? Answers to the aforementioned scenarios are somewhat elusive, but in general, they are explained by the presence or absence of risk factors that cause individuals to be vulnerable [4]. Some risk factors are external or environmental and related to ICU experience, while, alternatively, some of these risk factors are related to intrinsic characteristics. Events involving sedation [5] in the ICU are often associated with delirium and later onset of PTSD symptoms [6, 7], although the evidence in this regard is clearly not unequivocal. Moreover, memories of frightening psychotic experiences during ICU hospitalization have been associated with later PTSD symptoms [8]. While most researchers believe delusional memories are particularly likely to form the basis for PTSD in ICU survivors, not all investigations have supported this finding [9]. Younger age and pre-existing mental health diagnoses also confer increased risk of PTSD [10].

12.3 Epidemiology of PTSD in ICU Survivors

It has been estimated that somewhere between 10% and 50% of ICU survivors experience clinically significant symptoms of PTSD during the first year after ICU discharge [3]. If outliers are excluded, most studies estimate that PTSD occurs in between 20% and 30% of ICU survivors. This range is comparable to what is typically reported in American soldiers who experienced combat in Iraq or Afghanistan (23% according to a recent meta-analysis) [11]. Of note is the fact that PTSD is also very common in ICU patients' family members [12]. Symptoms experienced by family members and caregivers likely are related to communication and decision-making processes with the healthcare team and, more generally, to the profound trauma of watching their loved ones battle possible impending death over days, weeks, and sometimes months. Family members experiencing PTSD tend to possess a variety of risk factors, notably the existence of pre-existing mental health problems [13].

As a brief aside, although PTSD is often thought of in "all-or-nothing" terms, the truth, as most clinicians will attest, is far different than that, as symptoms of PTSD exist across a spectrum [14]. To be sure, the DSM-V provides a strict definition of PTSD which must be met for individuals to have a formal "PTSD" diagnosis. However, many individuals have isolated PTSD symptoms – very severe symptoms of avoidance, for example, in the absence of other symptoms – which can be profoundly debilitating even if they do not, strictly speaking, reflect PTSD. Avoidance, alone, may restrict an individual's ability to engage in future healthcare to reduce future adverse events such as rehospitalizations or limit medical adherence. It is unclear how many ICU survivors have isolated but problematic post-traumatic stress symptoms, but this number is likely quite large.

12.4 Biological Mechanisms of PTSD

A detailed treatment of issues related to biology is well beyond the scope of this chapter, but it is important to engage these issues, as biology is so central to PTSD. Briefly, stressful life situations contribute to an immediate "fight-or-flight" response which is anchored in concerns about survival. As a result, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are activated, leading to the release of catecholamines into the bloodstream. Even as this happens, the hypothalamus releases neuropeptides that, in turn, discharge cortisol, so that an individual's response to trauma is reduced, as homeostasis is restored. In some instances, however, dysregulation of the systems – collectively referred to as the "fear circuitry" – persists and symptoms of PTSD emerge, along with neurobiological abnormalities [15].

Key brain regions implicated in PTSD include the amygdala, the medial prefrontal cortex, and the hippocampus [16]. The amygdala appears to respond in an aggravated fashion in PTSD, leading to exaggerated reactions to fear and explaining the durability of traumatic memories. This dynamic is made possible by the fact that the medial prefrontal cortex – in contrast – is hyporesponsive, thus failing to inhibit the amygdala. With the combination of an overactive amygdala and a hyporesponsive prefrontal cortex, individuals likely experience limitations in their ability to regulate emotions while displaying deficits in attention and contextual processing. Reductions in hippocampal volume drive the creation of a range of cognitive deficits including problems separating past and present experiences.

12.5 Acute Stress in Critical Illness Survivors

Acute stress symptoms experienced during the course of ICU hospitalization are a risk factor for later development of PTSD [17]. Acute stress symptoms are PTSD symptoms that occur within the first month following exposure to a traumatic stressor, which may include exposure to the ICU environment, delirium, or the physical trauma prompting hospital admission [17]. Among survivors of critical illness, acute stress symptoms during ICU hospitalization following discharge are common among pediatric patients and their parents [18, 19], adult survivors of critical illnesses [20], relative caregivers of adult patients [12], and intensive care providers [21].

12.6 Unique Constellation of PTSD Symptoms in Critical Illness

While risk factors for the development of PTSD in ICU survivors are not particularly well studied, even less is known regarding the unique constellation of symptoms experienced by ICU survivors in comparison with the existing literature on risk factors for the development of PTSD in ICU survivors. Briefly, not all individuals with PTSD "look alike" – that is, even among individuals with a PTSD diagnosis, there are wide variations in clinical presentation. Even as we recognize this, it should be acknowledged that there are typical characteristics and behaviors that individuals report depending on the trauma they have experienced. For example, combat veterans with PTSD are frequently extremely "jumpy" and reactive to sounds. This translates into difficulties in certain activities that families often enjoy – e.g., problems attending fireworks shows on the 4th

of July, problems attending loud sporting events, as well as problems working in environments such as loud and noisy factories. Patients with PTSD due to a near drowning – to name just one trauma – likely don't have the same triggers and their reactivity may be expressed in different ways, in response to different things. In the same way, traumatized survivors of intensive care may have certain notable clinical features such as re-experiencing symptoms focused on preoccupation with future-oriented enduring threats of recurrence of the medical condition at hand rather than on a discrete event in the past whose danger has passed. Among individuals with PTSD following critical illness, avoidance symptoms – in our clinical experience – appear to be the most disruptive. Avoidant patients may display a reluctance to seek help, a denial of difficulties, and apprehension that disclosing problems to healthcare providers could lead to another ICU admission. For an example of typical PTSD symptoms among ICU survivors based on our anecdotal clinical experience, refer to ► Box 12.2.

Box 12.2: A Clinical Vignette of an ICU Survivor with PTSD

Colin spent 6 weeks in intensive care with sepsis, delirium, and multiple organ failure. During this time, he experienced vivid hallucinations and delusions as well as anxiety about his possible impending death. After discharge, he developed a strong preoccupation with his health and, in particular, became terrified of the prospect of having to be rehospitalized. This led to concerns about "germs" and resulted in decreased social interaction, particularly in the winter. He also refused to have a recommended ankle surgery – though it was quite minor *and* crucial for his continued physically demanding employment – due to worries about going "under anesthesia." He grappled with serious insomnia from regular nightmares of the many images he remembered in the midst of his delirium episodes – specifically, he reported being "haunted" by memories of a respiratory therapist trying to "cut off" his "wind pipe." A deacon at his small country church, he stopped "calling" on sick parishioners – though he has previously loved doing this – as he could not bear to visit the hospital where he received treatment.

12.7 Impact of Critical Illness PTSD on Healthcare Engagement

One key potential consequence of PTSD that develops against the backdrop of illness and hospitalization pertains to the way that healthcare is engaged in the future. Numerous studies have focused explicitly on the impact of medically related PTSD on healthcare engagement. In one of the first investigations to date, Newman and colleagues [22] found that cardiac patients with PTSD took 2.5 times longer to seek emergency assistance than without a diagnosis of PTSD (25.7 hours versus 10.7 hours, $p = 0.005$) and that the cognitive and emotional representations of symptoms were primary contributors. In another study, stroke survivors with PTSD symptoms were almost 300% more likely to be nonadherent to their prescribed medications as those without PTSD symptoms years after the index stroke event [23]. These studies highlight the impact of forward focused threats which serve as potent reminders of chronic disease, illness, or injury [24], thus preventing delivery and maintenance of care for patients who have developed PTSD after critical illness. Ironically, avoidance of care – whether simple care like a "well visit" or serious care involving surgery or inpatient treatment – may create a maladaptive cycle in which symptoms worsen because care is avoided, a dynamic which may lead to the development of even more severe anxiety, more serious illness, and, in some cases, death.

12.8 PTSD Assessment in the ICU and Beyond

Assessment of PTSD in the ICU is difficult, as critically ill patients typically experience problems with verbal communication as well as limited attention spans in a chaotic and distracting environment in which assessments occur. Therefore, assessment measures must be brief, easily administered, and easily understood. While PTSD is assessed in the ICU in rare cases, more typically it is evaluated at various follow-up intervals. One issue referenced in literature is that assessment of PTSD after critical illness tends to be nonstandardized, limiting our ability to definitively identify appropriate measures to use [25] and limiting our ability to make so-called "apples to apples" comparisons when comparing studies. This trend has been improving, however, with more studies using identical measures, allowing for more accurate comparisons across investigations [3]. In particular, the Impact of Events Scale-Revised (IES-R) and the Post-traumatic Stress Checklist (PCL) have also been widely employed [26, 27]. Both of these are brief screening measures; and, though robust assessment tools, they rely on patient self-report as opposed to clinician's insights and interpretation (which are often elicited in much longer and more comprehensive diagnostic interviews like the Clinician Administered PTSD Scale, a much more sensitive clinical tool but one that can take between 90 and 120 minutes to administer) [28]. Some screening tools may result in high false-positive rates, reducing their clinical utility [25]; therefore, it is important to assess the psychometric properties and feasibility of their use with patients who are critically ill.

12.9 PTSD Interventions in the ICU

Despite the high prevalence of critical illness related PTSD, there have been very few studies on non-pharmacologic interventions [29] that could prevent PTSD, and there is no standard protocol for acute stress intervention in the setting of critical illness and ICU care. Among the few studies conducted to date, Peris and colleagues evaluated psychological outcomes of two cohorts of trauma ICU patients, treated either prior to or following the use of an in-ICU intervention by a clinical psychologist [30]. Those receiving the intervention reported a substantially lower prevalence of PTSD symptoms (21% vs. 57% at 12-month follow-up). The intervention addressed the psychological needs not only of patients but also their caregivers (typically relatives). In particular, the intervention emphasized stress management which involved cognitive and emotional restructuring, well-known approaches from the world of clinical psychology in which individuals learn to identify and challenge stressful thoughts. On average, patients received five or six interventions during their critical illness, all delivered by a clinical psychologist. The structure of the intervention highlights a transition from an independent model of care to an interprofessional plan of care that is collaborative and patient-centered.

Included in the recommended psychological treatments are cognitive-behavioral based therapies (CBT), eye movement desensitization and reprocessing (EMDR), and exposure treatments of various kinds [31]. Of these therapies, exposure therapy or combinations of exposure with cognitive therapy or stress inoculation training have the most robust evidence and are recommended as a first-line treatment for PTSD [32]. These approaches have not yet been tested in the ICU or specifically with survivors of critical illness. However, there are some recent studies to suggest that these strategies, and that exposure techniques, including brief prolonged exposure and virtual reality, may be

beneficial for treatment of early signs of PTSD and, therefore, prevention of long-term adverse outcomes [33]. Because the most salient symptom in critical illness survivors appears to be avoidance, cognitive behavioral techniques which include exposure therapy could be beneficial. Additional studies of in-ICU psychological interventions that study variables thought to facilitate or hinder recovery from critical illness, utilizing a patient-centered and collaborative team approach, are crucial and should be pursued.

12.10 PTSD Prevention

While there is limited research on *treatment* of PTSD in ICU survivors, one intervention that has been studied for *prevention* of ICU-related PTSD is the use of ICU diaries. ICU diaries are a written daily account of procedures and the patient's progress [34]. They are written by hospital staff and family members in everyday language and are presented to the patient in order to assist with developing an accurate narrative of intensive care hospitalization [35] and to increase understanding. Several studies have shown positive effects of ICU diaries for PTSD prevention, and improved quality of life, in survivors of critical illness and their family members, though debate about their effectiveness is ongoing as other investigations have been less supportive [34–36]. Other PTSD-related interventions evaluated for use in the ICU have been less direct, and few studies to our knowledge have targeted PTSD in ICU survivors after discharge (although at least one investigation is ongoing targeting acute stress) [37].

12.11 Long-Term Outcomes Associated with PTSD

In some cases, investigations of PTSD in ICU survivors have been done over an extended period of time, but, more typically, these investigations have been done with patients in the first year after their critical illness. Information that is available suggests that PTSD often persists for many years after hospitalization [25] and is associated with a variety of difficulties including cognitive impairment [38] and reduced health-related quality of life, although the directionality and nature of these associations remain unclear. It could be, as we've noted elsewhere, that PTSD can fundamentally change the brain in such a way that induces cognitive impairment or, alternatively, that individuals with cognitive impairment have particular susceptibility to experiencing and understanding trauma in a way that leads to PTSD. Patients with delusional memories that occur during or are associated with ICU hospitalization are at high risk of developing PTSD (a clinically relevant finding that has helped contribute to evolving approaches to in-hospital care that emphasize decreasing sedation and enhancing awareness as well as reducing the duration and severity of delirium) [39]. Patients with a history of panic attacks, agoraphobia, general anxiety symptoms, or depressive symptoms have been shown to be at higher risk of experiencing paranoid delusions and hallucinations in the ICU than patients without such a history [39].

12.12 Post-traumatic Growth in Survivors of Critical Illness

In the mid-1990s, psychologists Richard Tedeschi, PhD, and Lawrence Calhoun, PhD, developed a construct now known as post-traumatic growth (PTG), which refers to a widely observed phenomenon in which individuals experience a meaningful degree of

personal growth and development following exposure to a traumatic situation [40]. This is not to imply that trauma is at all a good thing, but rather, that for some people, it is a facilitator of transformation and growth. In particular, this growth is thought to occur in areas including appreciation of life, relationships with others, new possibilities in life, personal strength, and spiritual change. Although similar, PTG should not be confused with resilience, which refers more to a set of intrinsic personality traits that tend to exist in individuals who are remarkably sturdy and often unphased even by exposure to events which would derail the lives of most people. In our clinical experience, many ICU survivors report (often long after discharge) that, upon reflection, undergoing and surviving critical illness is transformative for them in key respects. That is, they value their relationships more deeply, take less for granted, experience a quality of gratitude that did not exist to the same degree before, place less importance on material things, etc. This dynamic at its core represents a fundamental shifting of belief systems about self, others, and the world and represents the essence of PTG, and people who achieve this likely have better outcomes. A crucial goal, then, relates to how to facilitate or teach PTG in individuals and their family members after critical illness.

12.13 The Unique Stresses of Critical Illness: The Role of Mental Health Professionals?

Critical illnesses and ICU hospitalization can be particularly stressful to patients, caregivers, and hospital staff and against this backdrop; the potential role of psychology, psychiatry, social work, and mental health, more generally, should be considered. Mental health professionals are trained to provide ecologically valid assessments and supportive services in a team-based environment, with a focus on assisting individuals with newly acquired disabilities and health-related limitations to adjust to new limitations and form new identities. In many cases, they possess a diversity of clinical skills that allow them to engage the complexities of ICU patients and survivors – skills in neuropsychological assessment, treatment planning, and in helping individuals develop compensatory strategies for dealing with newly acquired cognitive and emotional changes. To date, there have been limited studies to evaluate the role of the mental health professionals in intensive care settings – as consultants or members of the treatment team. Additional studies are needed to determine the ideal role of mental health experts and to develop "best practice" guidelines for assessment, prevention, and treatment of PTSD in the critical care environment. Yet another point of integration for psychologists, psychiatrists, and others involves ICU recovery centers, specialty multidisciplinary clinics dedicated to the assessment and treatment of individuals with post-intensive care syndrome (PICS) following critical illness [41]. Such clinics, which have emerged in North America in the last 5 years or so (though they have been present in the United Kingdom for some time), vary widely in their approaches to patient care. In general, however, they target individuals with critical care-related sequelae including PTSD. One potential benefit of treating individuals in the post-discharge space is that their symptoms may have concretized to a degree – that is, medical providers know what they are dealing with because symptoms are no longer transient to the extent that they likely were at or around the time of hospital discharge. As such, mental health conditions can be targeted more confidently.

12.14 PTSD in ICU Survivors: A Modest Research Agenda

Approximately a quarter century of research has been done on PTSD in ICU survivors, and this has resulted in the generation of important insights that have benefited individual patients and their families while improving public health more generally. While much has been done, key issues remain, and while these would require an entire chapter of their own to even begin to engage, we will list a few of them here:

1. Developing ways to identify patients at highest risk for PTSD and identifying systems that help target them for treatment.
2. Determining what strategies can be developed and utilized to help prevent acute stress disorder and PTSD in ICU patients.
3. Creating approaches to build and foster resilience in ICU survivors with PTSD – these individuals frequently return to the ICU, and the development of resilience may help them withstand the adverse mental health effects of critical illness.
4. Focusing on helping traumatized individuals and their frequently traumatized family members experience post-traumatic growth.
5. Understanding more fully the biological mechanisms that undergird the development of PTSD after critical illness.

Conclusions

PTSD is common in survivors of critical illness and, according to some studies, occurs at rates comparable to those seen in groups such as combat veterans, though estimates about the prevalence vary widely. While research has focused on characterizing the prevalence of this syndrome as well as identifying risk factors, it remains unclear whether there are clinical distinctives that may be uniquely characteristic in patients after ICU care. One key goal of future research efforts is to engage this question – that is, whether there are specific symptoms of PTSD secondary to critical illness that can be clinical targets. Theoretical suggestions and limited evidence have suggested the potential prominence of avoidant symptoms, coupled with delusional memories and a fixation on future rather than past trauma. While the nature of PTSD symptoms after critical illness needs to be studied further, it is not too soon to begin thinking critically about the ways that clinical interventions could target specific symptoms, such as intense fear of recurring illness and an irrational fear of hospitalizations or surgery. The potentially unique clinical profile of PTSD after critical illness requires unique assessment and treatment practices for which empirical support at present is sparse, and both current and future patients will be well served by research that focuses on developing innovative approaches to evaluation and tailored approaches to treatment.

Take-Home Messages

- PTSD is common in survivors of critical illness and represents a major public health problem.
- PTSD in survivors of critical illness may have a unique clinical expression and is reflected in avoidance of engagement in healthcare-related activities.
- A portion of survivors of critical illness – regardless of PTSD status – experience post-traumatic growth and experience positive changes that they attribute to the effects of their trauma.
- Models of care that integrate mental health professionals into the management of ICU survivors with PTSD appear to be promising and deserve greater integration.

References

1. Crocq MA. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. Dialogues Clin Neurosci. 2000;2(1):47–55.
2. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit Care. 2013;17:R81.
3. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a meta-analysis. Crit Care Med. 2015;43(5):1121–9.
4. Elwood LS, Hahn KS, Olatunji BO, Williams NL. Cognitive vulnerabilities to the development of PTSD: a review of four vulnerabilities and the proposal of an integrative vulnerability model. Clin Psychol Rev. 2009;29(1):87–100.
5. Pandharipande P, Shintani A, Peterson J, Pun B, Wilkinson G, Dittus R, Bernard GR, Ely E. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
6. Girard T, Shintani A, Jackson J, Gordon S, Pun B, Henderson M, Dittus RS, Bernard GR, Ely E. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care. 2007;11(1):28.
7. Samuelson K, Lundberg D, Fridlund B. Stressful memories and psychological distress in adult mechanically ventilated intensive care patients – a 2-month follow-up study. Acta Anaesthesiol Scand. 2007;51(6):671–8.
8. Rattray J, Johnston M, Wildsmith J. Predictors of emotional outcomes of intensive care. Anaesthesia. 2005;60:1085–92.
9. Granja C, Gomes E, Amaro A, Ribeiro O, Jones C, Carneiro A, for the JMIP Study Group. Understanding posttraumatic stress disorder-related symptoms after critical care: the early illness amnesia hypothesis. Crit Care Med. 2008;36:2801–9.
10. Marra A, Pandharipande P, Patel M. Intensive care unit delirium and intensive care unit-related posttraumatic stress disorder. Surg Clin North Am. 2017;97(6):1215–35.
11. Fulton JJ, Calhoun PS, Wagner HR. The prevalence of posttraumatic stress disorder in operation enduring freedom/operation Iraqi freedom (OEF/OIF) veterans: a meta-analysis. J Anxiety Disord. 2015;31:98–107.
12. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, Annane D, Bleichner G, Bollaert PE, Darmon M, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171(9):987–94.
13. Petrinec AB, Daly BJ. Post-traumatic stress symptoms in post-ICU family members: review and methodological challenges. West J Nurs Res. 2016;38:57–78.
14. C M, Zisook S. Rationale for a posttraumatic stress spectrum disorder. Clin North Am. 2002;25(4):775–90.
15. Sherin JE, Nemeroff CB. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues Clin Neurosci. 2011;13:263–78.
16. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci. 2006;1071:67–79.
17. Davydow DS, Zatzick D, Hough CL, Katon WJ. A longitudinal investigation of posttraumatic stress and depressive symptoms over the course of the year following medical–surgical intensive care unit admission. Gen Hosp Psychiatry. 2013;35(3):226–32.
18. Kaplan D, Nkromah T, Eldridge P, Mennella J, Ansari N, Li S, Whyte-Nesfield M. Acute stress in patients and caregivers of patients admitted to the intensive care unit. Crit Care Med. 2018;46:417.
19. Shaw RJ, Deblois T, Ikuta L, Ginzburg K, Fleisher B, Koopman C. Acute stress disorder among parents of infants in the neonatal intensive care nursery. Psychosomatics. 2006;47:206–12.
20. Davydow DS, Zatzick D, Hough CL, Katon WJ. In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission. Ann Am Thorac Soc. 2013;10(5):450–45.
21. Mealer ML, Shelton A, Berg B, Rothbaum B, Moss M. Increased prevalence of post-traumatic stress disorder symptoms in critical care nurses. Am J Respir Crit Care Med. 2007;175(7):693–7.
22. Newman J, Muntner P, Shimbo D, Davidson K, Shaffer J, Edmondson D. Post-traumatic stress disorder (PTSD) symptoms predict delay to hospital in patients with acute coronary syndrome. PLoS One. 2011;6(11):e2764.

23. Kronish I, Edmondson D, Goldfinger J, Fei K, Horowitz C. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. Stroke. 2012;42(8):2192–7.
24. Edmondson D. An enduring somatic threat model of posttraumatic stress disorder due to acute life-threatening medical events. Soc Personal Psychol Compass. 2014;8(3):118–34.
25. Jackson JC, Hart RP, Gordon SM, Hopkins RO, Girard TD, Ely EW. Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. Crit Care. 2007;11(1):R27.
26. Patel MB, Jackson JC, Morandi A, et al. Incidence and risk factors for intensive care unit-related post-traumatic stress disorder in veterans and civilians. Am J Respir Crit Care Med. 2016;93(12):1373–81.
27. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosom Med. 2008;70:512–9.
28. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8:75–90.
29. Wade DF, Moon Z, Windgassen SS, AM H, Morris L, Weinman JA. Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. Minerva Anestesiol. 2016;82(4): 465–47.
30. Perier A, Revah-Levy A, Bruel C, Cousin N, Angeli S, Brochon S, Philippart F, Max A, Gregoire C, Misset B, Garrouste-Orgeas M. Phenomenologic analysis of healthcare worker perceptions of intensive care unit diaries. Crit Care. 2013;17(1):R13.
31. Forbes D, Creamer M, Bisson JI, Cohen JA, Crow BE, Foa EB, Friedman MJ, Keane TM, Kudler HS, Ursano RJ. A guide to guidelines for the treatment of PTSD and related conditions. J Trauma Stress. 2010;23(5):537–52.
32. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin Psychol Rev. 2010;30(6):635–41.
33. Leaman SC, Kearns MC, Rothbaum BO. Prevention and early intervention: PTSD following traumatic events. Focus J Lifelong Learn Psychiatry. 2013;11(3):321–7.
34. Bäckman CG, Walther SM. Use of a personal diary written on the ICU during critical illness. Intensive Care Med. 2001;27(2):426–9.
35. Egerod I, Christensen D, Schwartz-Nielsen KH, Agard AS. Constructing the illness narrative: a grounded theory exploring patients' and relatives' use of intensive care diaries. Crit Care Med. 2011;39(8): 1922–8.
36. Knowles RE, Tarrier N. Evaluation of the effect of prospective patient diaries on emotional Well-being in intensive care unit survivors: a randomized controlled trial*. Crit Care Med. 2009;37(1):184–91.
37. Wade D, Als N, Bell V. Providing psychological support to people intensive care: development and feasibly study of a nurse-led intervention to prevent acute stress abd long term morbidity. BMJ Open. 2018;8:e021083.
38. Horner MD, Hamner MB. Neurocognitive functioning in posttraumatic stress disorder. Neuropsychol Rev. 2002;12(1):15–30.
39. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001;29(3): 573–80.
40. Tedeschi RG, Calhoun LG. Post-traumatic growth: conceptual foundations and empirical evidence. Psychol Inq. 2004;15:1–18.
41. Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU survivors: development and implementation of an ICU recovery center. J Crit Care. 2018;46:141–8.

Mood Disorders and Dementia in Survivors of Intensive Care

Lavarnan Sivanathan and Hannah Wunsch

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_13

Learning Objectives

- Describe mood disorders after critical illness.
- Provide an overview of the epidemiology of mood disorders in ICU survivors.
- Describe the assessment of pre-ICU mood disorders.
- Discuss factors associated with mood disorders after critical illness.
- Review the pathophysiology of mood disorders after ICU.
- Discuss the interventions for ICU survivors with mood disorders after discharge from ICU.
- Provide an overview of the epidemiology of dementia and long-term cognitive dysfunction in ICU survivors.
- Identify factors associated with dementia disorders after critical illness.

13.1 Mood Disorders and Dementia After Critical Illness

Due to improved care and reduction of mortality of ICU patients combined with an aging population, more patients than ever before are being admitted to and surviving a stay in ICU [1]. Historically, critical care physicians noted mental disorders along with physical and cognitive dysfunctions that complicated the recovery process after ICU [2, 3]. These descriptions included well-defined mental illness diagnoses as well as less specific psychological symptoms including insomnia, impaired memory, hallucinations, flashbacks, recurrent nightmares, and feelings of guilt. These descriptions have also included cognitive impairment severe enough to be defined as dementia. The idea of a common constellation of problems encountered by intensive care survivors was defined as the "post-intensive care syndrome" (PICS) [4]. PICS includes three domains: mental illness, cognitive impairments, and physical impairments.

13.2 The Epidemiology of Mood Disorders in ICU Survivors

Mental illness after ICU primarily consists of mood disorders, generalized anxiety disorders, and post-traumatic stress disorder (PTSD) [5]. Although all have been assessed, recent research suggests that mood disorders may impact more patients than PTSD [6]. The approach to assessing patients for mood disorders has a large impact on the reported incidence or prevalence. The majority of cohort studies use structured interviews or questionnaires to assess mood disorder symptoms rather than identifying specific diagnoses. Alternatives include psychiatric diagnoses from healthcare data and prescriptions for psychiatric medications.

In a 2009 systematic review of depression after a critical illness by Davydow et al. that included 14 studies (n = 1213 ICU survivors), the median point prevalence of clinically significant depressive symptoms among survivors was 28% (range 8–57%) 2 months after hospital discharge [7]. The primary questionnaire used in the majority of included studies (8/14) was the Hospital Anxiety and Depression Scale (HADS) [7]. Among the studies included in the review, the occurrence of depressive symptoms ranged from 7.5% in a Swedish study of 226 ICU survivors (using the HADS) up to 60% in 2 studies using the Center for Epidemiologic Studies Depression Scale (CES-D) [8–10].

In the more recent BRAIN-ICU cohort, a large prospective multicenter cohort study of 821 patients (with only 47% follow-up), 33% of those who were followed up met criteria for depression at 12 months. However, it was notable that this study used the Beck Depression Scale rather than the HADS [6]. The authors comment that many of the scores above the cutoff for depression were driven by the physical symptoms assessed as part of the depression screening and raise the possibility that this may be more indicative of physical disability [6]. The use of the HADS, rather than other depression scales, for detection of depressive symptoms among ICU survivors may be important, as it was specifically designed to exclude somatic symptoms so that it could be used in patients with physical illnesses [11, 12].

Using psychiatric diagnoses by psychiatrists, a Danish study of ICU survivors who had no prior history of psychiatric illness and received mechanical ventilation (n = 24,717) reported that only 0.5% of ICU survivors had a new psychiatric diagnosis in the year after hospital discharge [13]. However, use of psychiatric medications, such as antidepressants, was substantially higher (12.7%) suggesting that many patients may be diagnosed and cared for by nonpsychiatrists (e.g., general practitioners) [13]. In the same study, a comparison was made to hospitalized individuals who did not require intensive care, and the general population. Rates of diagnoses for ICU survivors were higher than for matched hospitalized patients and general population at 3 and 6 months; by 1 year, rates were higher than in the general population, but no different from hospital controls, suggesting that some of the "post-intensive care syndrome" may, in fact, overlap with a more general "posthospital syndrome" [14].

13.3 Accurate Assessment of Pre-ICU Mood Disorders

One challenge of interpreting rates of mood disorders is understanding how often they are new diagnoses versus a chronic condition. Patients who are admitted to the ICU are different from the general population and therefore may have a higher prevalence of mood disorders even before a critical illness [15]. Many studies are limited in their ability to account for pre-existing mood disorders among ICU survivors [16], and some or most of the burden of mental illness after ICU may not be related to the critical illness. The Danish administrative study mentioned above excluded patients with previous mood disorders and only accounted for new incidence of mental illness in ICU survivors [13]. Additionally, in a study of Americans over the age of 50 who had severe sepsis (n = 439), the prevalence of mood disorders before and after the episode of severe sepsis remained high (at 28%) [15]. However, it is important to note that all patients, irrespective of the timing of onset or cause, are still in need of adequate mental health follow-up.

13.4 Factors Associated with Mood Disorders After Critical Illness

Multiple studies of ICU patients have examined factors associated with a higher risk of having a mood disorder after hospital discharge. Risk factors assessed can be divided into patient characteristics and ICU-associated factors. Patient characteristics are generally fixed and therefore difficult or impossible to modify in the ICU environment, but are

useful for identifying high-risk subgroups. Three distinct populations of ICU patients have been examined in these studies. The first is the heterogenous population of all ICU patients, the second is patients with lung pathology such as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), and the third is patients with infection and/or sepsis [15, 17, 18].

Most studies that have assessed patient characteristics have examined the heterogenous population of all ICU survivors [10, 19]. Patient characteristics, such as a previous diagnosis of a mental illness, female sex, alcohol dependence lower socioeconomic status, and younger age, have all been associated with depression after hospital discharge across a range of cohort studies [7, 10, 18–20]. ICU-associated factors identified include the receipt of benzodiazepines during the hospitalization [18], episodes of hypoglycemia [21], and sleep disruption [22]. High levels of stress or scores on depression screening questionnaires at discharge or shortly after discharge (5 days) have also been associated with depressive symptoms at 2 months after discharge [10]. Of note, in a cohort study of 567 ICU survivors, delirium was not found to be associated with depression [23].

Two studies have specifically looked at factors associated with the development of mood disorders in patients with lung pathology. The first study had a 1-year follow-up of 66 mechanically ventilated patients with ARDS [17] and identified alcohol dependence, female sex, and younger age as factors associated with depression at 1 year (using the Beck Depression Inventory) [17]. Another study focusing on 104 ALI survivors found that a recorded mean ICU glucose of less than 100 mg/dL was associated with a positive depression screen (HADS) at 3 months after discharge. The study also found that hypoglycemic readings (glucose <60 mg/dL) were associated with higher depression scores [21]. Finally, the study identified ICU dose(s) greater than 100 mg of midazolam-equivalent benzodiazepine, baseline depression and anxiety, and BMI above 40 as all associated with a positive depression screen [21].

One study that included patients with pre-ICU depressive symptoms examined factors associated with depressive symptoms after severe sepsis [15]. They found no association of the incident severe sepsis with subsequent depressive symptoms. However, they did find that pre-ICU depressive symptoms (relative risk (RR) 2.20, 95% CI, 1.66–2.90) and worse post-sepsis functional impairment (RR 1.98 per limitation, 95% CI, 1.03–1.13) were independently associated with substantial depressive symptoms following sepsis [15].

13.5 Pathophysiology of Mood Disorders After ICU

Of the risk factors described above, two that are ICU-related (exposure to benzodiazepines and hypoglycemia) have possible mechanistic explanations that have recently been described. Benzodiazepines modulate gamma-aminobutyric acid (GABA)-A receptors, the most common inhibitory neurotransmitter in the central nervous system. These receptors are found abundantly in the limbic system, which modulates mood [24]. Benzodiazepines work through the potentiation of the GABA-A receptors and have been associated with depression as well as cognitive dysfunction [18, 21]. Studies conducted in rats have shown that benzodiazepines also cause neurodegeneration [25]. Specifically, the histological slides of rat brains after exposure to benzodiazepines demonstrated apoptotic neurodegeneration [25].

Hypoglycemia causes a distinctive pattern of neuronal cell death unlike brain ischemia [26]. The dentate gyrus of the hippocampus, which is important for mood regulation,

along with the superficial layers of the cortex is very sensitive to hypoglycemia-induced neuronal necrosis. This cell necrosis is mediated by aspartate efflux out of the cell causing calcium fluxes that rapidly lead to necrosis. The cerebellum and the brainstem are spared in hypoglycemic brain damage, keeping the vital life-maintaining functions of these regions intact [26].

13.6 Interventions for ICU Survivors with Mood Disorders

It is important to note that some physical diagnoses or symptoms may be associated with, or mimic, depression and should be assessed in conjunction with any concern regarding a diagnosis of a mood disorder. For example, anemia, neuromuscular disorders, cardiovascular disease, mobility issues, and endocrinological pathology can all cause depressive symptoms that can be resolved by addressing the underlying medical problem [3]. Appropriate history, physical exam, and laboratory tests can diagnose medical causes of many of the symptoms of depression, and subsequent treatment or referral to appropriate specialists may be helpful [3].

During the ICU stay, minimizing modifiable risk factors that are known to be associated with mood disorders after discharge, such as hypoglycemia and exposure to benzodiazepines, may result in lower rates of mood disorders in ICU survivors [18, 21]. However, it is important to note that while these risk factors have plausible mechanistic explanations, no intervention studies have specifically demonstrated an improvement in mood disorders with modification of these exposures.

Awareness by physicians encountering ICU survivors after discharge of mood disorders and the benefits of early intervention may be important in order to initiate any early intervention [2]. However, studies of close follow-up after hospital discharge have yielded mixed results [27, 28]. Three studies have examined follow-up of patients after hospital discharge and have not demonstrated improvements in mood disorder outcomes [27–29]. The RAPIT study by Jensen et al. was a pragmatic, non-blinded, multicenter, parallel-group randomized controlled trial (RCT) with 190 patients in each arm that examined a nurse-led intensive care recovery program for ICU survivors [28]. The study showed no significant difference between the interventional group and the controls group when they assessed HADS score for depression at 12 months after discharge [28].

Another small prospective, quasi-experimental non-blinded single-center study of nurse-led follow-up with only 13 patients in the experimental group and 72 in the control group also found no difference in the incidence of mental illness after ICU between both groups [27]. Finally, an RCT of 175 patients examined an educational program from psychologists for ICU survivors after discharge compared to a control group who had primarily videos explaining PICS symptoms and recovery [29]. The psychologist interventional group received six weekly 30-minute telephone sessions from a psychologist, while the control group had access to videos and received two 30-minute sessions with a content expert in the videos. They found that the CST did not improve psychological distress compared to the education program [29]. However, in patients with high baseline distress, the CST improved symptoms of distress at 6 months, while the education program improved distress at 3 months among patients on a ventilator for greater than 7 days [29].

There are multiple reasons these follow-up strategies may not have shown benefit. First, some experts advocate starting the screening process and interventions as early as when patients are moved to the ward from ICU [2]. Second, the intensity of the interven-

tion may not be sufficient. For example, a 30-minute session with a psychologist may not be adequate to develop coping strategies for a mood disorder. Third, most of these studies are small and may lack the power to demonstrate an effect. Finally, the patients in these studies are a heterogenous group and the signal from high-risk ICU survivors who develop mood disorders may be attenuated by the other ICU survivors who are at lesser risk. These issues may be overcome by selecting an enriched population of ICU survivors who have specific risk factors for developing mood disorders, by ensuring that the ICU survivors enrolled do not have a medical or physiological derangement causing the mood symptoms, and by ensuring there is a large enough sample size to detect the impact of the intervention.

The role of antidepressants for treatment of ICU survivors with symptoms of depression is unexplored. It is clear that antidepressants are being prescribed to individuals after critical illness [13], but their utility either for early treatment of depression symptoms in the ICU or after discharge has not been assessed. A pilot retrospective cohort study that had follow-up data of only 27 patients prescribed antidepressants de novo while in the ICU found no statistical difference in the rates of post-ICU depression compared to historical controls [30]. Much more data are needed with larger studies to determine the utility of medication in this population.

Physical therapy may also play a role in improving mood symptoms of ICU survivors. ICU survivors may be experiencing mobility issues, and this can limit their ability to work, their social activities, and their independence [20]. While purely speculative, by improving their physical function and mobility issues and therefore improving engagement in many aspects of their life, ICU survivors could also have improvement in mood symptoms [20].

13.7 Dementia

While mood disorders may be transient, dementia is a progressive, irreversible clinical syndrome that is a result of widespread impairment of mental function [31]. Yet anecdotally, similar to mood disorders, incidence rates increase after an admission to ICU, as many people view critical illness as a "trigger" resulting in cognitive dysfunction and a downward spiral to dementia.

In Western countries 3–10% of people over 65 years of age have dementia and over 46 million are affected worldwide [32, 33]. Dementia is difficult to diagnose especially in the early stages and when it is mild due to the insidious and variable onset of the syndrome [32]. Family members also take over social roles of the patients, protecting them from obstacles in daily life and as a result may delay the diagnosis of dementia [32]. Due to these factors, detecting the incidence of new dementia remains difficult.

The *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-V) elaborates on the diagnosis of dementia as having problems with seven domains: complex attention, executive function, learning and memory, language, perceptual-motor function, language, and social cognition [34]. Dementia is diagnosed by history taking, cognitive and mental state examination, physical examination, and review of medications [31]. There are various dementia rating scales that screen for or rank severity of dementia from mild to severe based on these seven domains and functionality [35]. The most well-known are the Global Deterioration Scale (GDS), Clinical Dementia Rating (CDR), and the Mini-Mental State Examination (MMSE) [35].

There are several difficulties associated with assessing rates of dementia after critical illness. First, there may be ICU-acquired cognitive impairment that is stable (i.e., not progressive) yet is not severe enough to be considered dementia. Second, undiagnosed dementia may have been present prior to the critical illness but only detected when screened after ICU discharge. Third, a true diagnosis of dementia requires in-depth assessment that may be challenging after a critical illness associated with other disability or disease [36]. Reversible causes of cognitive dysfunction such as delirium and medical causes should be ruled out prior to a dementia diagnosis [31]. Structural imaging should also be conducted to rule out other causes of brain pathology [31]. However, assessment of dementia after critical illness is important since an increasing number of patients being admitted to the ICU are elderly and dementia is a large concern for these patients and their families [37, 38].

13.8 Epidemiology of Dementia in ICU Survivors

Admission to the ICU may be associated with an increased risk of dementia, but the majority of work has focused on cognitive impairment rather than specifically dementia. The prevalence estimates of long-term cognitive dysfunction after ICU range widely [39, 40]. In a study of elderly individuals in the United States, rates of cognitive impairment were increased after a hospitalization with severe sepsis, but specific diagnoses of dementia were not reported [41]. Moreover, there was no "dose response" for those who had a severity of illness necessitating ICU admission. Further, a large prospective study found that 6% of patients enrolled had pre-existing mild cognitive dysfunction, and up to 24% of the ICU survivors had significant cognitive dysfunction that were similar to scores obtained by patients with mild Alzheimer's dementia 12 months after discharge [42]. Of note, those with severe pre-existing cognitive dysfunction were excluded from the study. A study that looked at 55 ARDS patients found that 30% of them had cognitive decline 1 year after discharge and all patients had cognitive dysfunction based on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) at the time of discharge [43]. Cognitive dysfunction in one domain such as memory, attention, or concentration was present in 78% patients 1 year after discharge [43].

These epidemiological studies have shown an increase in long-term cognitive dysfunction after ICU, although the causal factors for this trend are still being explored. Very few studies have assessed actual dementia. One study of 2929 individuals 65 years or older found incident dementia was increased in individuals hospitalized (adjusted hazard ratio (aHR) 1.4, 95% CI, 1.1–1.7) and was even higher for individuals following a critical illness (aHR 2.3, 95% CI, 0.9–5.7), although the numbers with a critical illness were very small [39]. Another larger study of 25,368 Medicare patients (>65 years of age) in the United States assessed diagnoses of dementia in the 3 years following an ICU admission. These individuals had a 15.0% incidence of a diagnosis of dementia. This was compared with general population controls who were age, sex, and race matched, who had an incidence of 12.2%. Although the adjusted hazard ratio for an increased risk after ICU admission was high (1.43, 95% CI, 1.32–1.54), the absolute difference in 3-year incidence was only 2.8% [38]. It is important to note that this study likely underestimated dementia rates in both the ICU and general population groups, as it relied on healthcare record diagnoses of dementia rather than an in-depth assessment of all individuals. Further studies assessing dementia rates are an area for future research.

13.9 Factors Associated with Dementia After ICU

Dementia incidence doubles every 5 years from age 65 to 90 in the general population [44]. Increasing age is certainly associated with higher risk of dementia in ICU survivors [38]. However, it is notable in the Medicare study described above that the risk relative to general population controls was consistent across age bands, suggesting no interaction between age and intensive care.

The cohort study by Pandharipande et al. of 821 patients with 1-year follow-up identified the length of neurological dysfunction during ICU admission as a risk factor associated with the development of long-term cognitive dysfunction [42]. This is similar to the signal for an increased risk of a diagnosis of dementia associated with neurological dysfunction during the hospitalization found in the Medicare cohort [38]. Other factors identified in this same study included diagnoses of infection or sepsis and receipt of (new) acute dialysis.

It is notable that multiple studies have failed to show an association between severity of illness in ICU and subsequent neurocognitive impairments or diagnosis of dementia. The severity of illness has been assessed in many ways, including Acute Physiology and Chronic Health Evaluation (APACHE) II score, duration of mechanical ventilation, and the number of days in ICU [38, 40, 45, 46]. Finally, despite concerns regarding a relationship between receipt of sedatives such as benzodiazepines and development of delirium in hospital [47], the number of days receiving sedative(s), narcotic, or paralytic medication was not associated with long-term cognitive impairment [40, 45, 46]. Specifically, more recent work by Pandharipande et al. did not demonstrate a relationship between receipt of benzodiazepines and long-term cognitive dysfunction [42]. These studies demonstrate the complexity of potential exposures and the challenges of assessment of cognitive outcomes and long-term follow-up. Large, longitudinal studies are still needed for further exploration of this important area.

13

Take Home Messages

Mood Disorder in ICU Survivors

- Up to 30% of ICU survivors may experience mood disorders after discharge.
- Most studies of post-ICU mood disorders do not adequately differentiate between ICU-associated mood disorders and pre-existing conditions.
- Somatic symptoms related to physical weakness and disability may be contributing to higher scores on assessment for mood disorders.
- The majority of ICU survivors are not assessed by psychiatrists and few receive specific diagnoses of mood disorders.
- Patient risk factors for mood disorders in ICU survivors include the following: a previous diagnosis of a mental illness, female sex, previous alcohol dependence, body mass index (BMI) >40, lower socioeconomic status, and younger age.
- ICU risk factors for mood disorders in ICU survivors include the following: benzodiazepines during the hospitalization, episodes of hypoglycemia, and sleep disruption.
- Studies to date of close follow-up by psychologist or nurses after discharge have not reduced the incidence of mood disorders in ICU survivors.

Take Home Messages

Dementia in ICU Survivors

- The majority of studies of follow-up of ICU patients assess cognitive dysfunction and not specific diagnoses of dementia.
- A large difficulty with studies of dementia related to critical illness is limited assessment pre-ICU regarding possible mild dementia.
- ICU risk factors associated with dementia after ICU include sepsis, infection, neurological dysfunction (delirium), and acute dialysis.
- Severity of illness and exposure to sedatives do not appear to be associated with subsequent cognitive dysfunction.

Financial Disclosure The authors have no commercial associations or financial disclosures to declare.

References

1. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc. 2012;60:1070–7.
2. Griffiths RD, Jones C. Recovery from intensive care. BMJ. 1999;319:427–9.
3. Volk B, Grassi F. Treatment of the post-ICU patient in an outpatient setting. Am Fam Physician. 2009;79:459–64.
4. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Otr L, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, et al. Improving long-term outcomes after discharge from intensive care unit. Crit Care Med. 2012;40:502–9.
5. Wade D, Page V. Long-term mental health after ICU, let's go through the looking glass. Crit Care Med. 2016;44:1934–5.
6. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, Pun BT, Vasilevskis EE, Morandi A, Shintani AK, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med. 2014;2:369–79.
7. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, Needham DM. Depression in general intensive care unit survivors: a systematic review. Intensive Care Med. 2009;35:796–809.
8. Boyle M, Murgo M, Adamson H, Gill J, Elliott D, Crawford M. The effect of chronic pain on health related quality of life amongst intensive care survivors. Aust Crit Care. 2004;17:104–13.
9. Guentner K, Hoffman LA, Happ MB, Kim Y, Dabbs AD, Mendelsohn AB, Chelluri L. Preferences for mechanical ventilation among survivors of prolonged mechanical ventilation and tracheostomy. Am J Crit Care. 2006;15:65–77.
10. Samuelson KAM, Lundberg D, Fridlund B. Stressful memories and psychological distress in adult mechanically ventilated intensive care patients – a 2-month follow-up study. Acta Anaesthesiol Scand. 2007;51:671–8.
11. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
12. Robert P, Carson Alan RG. ABC of psychological medicine: depression in medical patients. BMJ. 2002;325:149–52.
13. Wunsch H, Christiansen CF, Johansen MB, Olsen M, Ali N, Angus DC, Sørensen HT. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. JAMA. 2014;311:1133–42.

14. Krumholz HM. Post-hospital syndrome — an acquired, transient condition of generalized risk. N Engl J Med. 2013;368:100–2.
15. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. Am J Geriatr Psychiatry. 2013;21:887–97.
16. Davydow DS, Hough CL, Russo JE, Von Korff M, Ludman E, Lin EHB, Ciechanowski P, Young B, Oliver M, Katon WJ. The association between intensive care unit admission and subsequent depression in patients with diabetes. Int J Geriatr Psychiatry. 2012;27:22–30.
17. Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JF Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. Gen Hosp Psychiatry. 2010;32:147–55.
18. Wade DM, Howell DC, Weinman JA, Hardy RJ, Mythen MG, Brewin CR, Borja-Boluda S, Matejowsky CF, Raine RA. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. Crit Care. 2012;16:R192.
19. Rattray JE, Johnston M, Wildsmith JAW. Predictors of emotional outcomes of intensive care. Anaesthesia. 2005;60:1085–92.
20. Jutte JE, Erb CT, Jackson JC. Physical, cognitive, and psychological disability following critical illness: what is the risk? Semin Respir Crit Care Med. 2015;36:943–58.
21. Dowdy DW, Dinglas V, Mendez-Tellez PA, Bienvenu OJ, Sevransky J, Dennison CR, Shanholtz C, Needham DM. Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. Crit Care Med. 2008;36:2726–33.
22. McKinley S, Aitken LM, Alison JA, King M, Leslie G, Burmeister E, Elliott D. Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness. Intensive Care Med. 2012;38:627–33.
23. de Lange DW, Cremer OL, van Dijk D. Long-term mental health problems after delirium in the ICU. Crit Care Med. 2016;1–6.doi: https://doi.org/10.1097/CCM.0000000000001861.
24. Scheel-Krüger J, Magelund G, Olianas M. The role of GABA in the basal ganglia and limbic system for behaviour. Adv Biochem Psychopharmacol. 1981;29:23–36.
25. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23:876–82.
26. Auer RN. Hypoglycemic brain damage. Metab Brain Dis. 2004;19:169–75.
27. Jónasdóttir RJ, Jónsdóttir H, Gudmundsdottir B, Sigurdsson GH. Psychological recovery after intensive care: outcomes of a long-term quasi-experimental study of structured nurse-led follow-up. Intensive Crit Care Nurs. 2017;1(8):59. https://doi.org/10.1016/j.iccn.2017.06.001.
28. Jensen JF, Egerod I, Bestle MH, Christensen DF, Elklit A, Hansen RL, Knudsen H, Grode LB, Overgaard D. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. Intensive Care Med. 2016;42:1733–43.
29. Cox CE, Hough CL, Carson SS, White DB, Kahn JM, Olsen MK, Jones DM, Somers TJ, Kelleher SA, Porter LS. Effects of a telephone- and web-based coping skills training program compared to an education program for survivors of critical illness and their family members: a randomized clinical trial. Am J Respir Crit Care Med. 2017;197(1):66–78. https://doi.org/10.1164/rccm.201704-0720OC.
30. Haines D, Hild J, He J, Stun L, Ballew A, Green JL, Satterwhite L, Flynn BC. A retrospective, pilot study of de novo antidepressant medication initiation in intensive care unit patients and post-ICU depression. Crit Care Res Pract. 2017;2017:1–5.
31. National Institute for Health and Care Excellence (NICE). Dementia: supporting people with dementia and their carers in health and social care. Cg42. 2017. https://www.nice.org.uk/guidance/cg42/resources/dementia-supporting-people-with-dementia-and-their-carers-in-health-and-social-care-pdf-975443665093%0A https://www.nice.org.uk/guidance/CG42/chapter/1-Guidance#diagnosis-and-assessment-of-dementia.
32. Burns A, Iliffe S. Dementia. BMJ. 2009;338:405–9.
33. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer report 2015 the global impact of dementia. London, UK: Alzheimer's Disease International (ADI); 2015. p. 1–82.
34. DSM-V. DSM-V American Psychiatric Association. Diagnostic and statistical manual of mental disorders, (DSM-5). 5th ed. Arlington: American Psychiatric Association; 2013.
35. Choi YJ, Won CW, Kim S, Choi HR, Kim BS, Jeon SY, Kim SY, Park KW. Five items differentiate mild to severe dementia from normal to minimal cognitive impairment – using the global deterioration scale. J Clin Gerontol Geriatr. 2016;7:1–5.

36. Hopkins RO. The brain after critical illness: effect of illness and aging on cognitive function. Crit Care. 2013;17:1–2.
37. Nguyen Y-L, Angus DC, Boumendil A, Guidet B. The challenge of admitting the very elderly to intensive care. Ann Intensive Care. 2011;1:29.
38. Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors for dementia after critical illness in elderly Medicare beneficiaries. Crit Care. 2012;16:R233.
39. Ehlenbach WJ, Hough CL, Crane PK, JPA Haneuse S, Carson SS, Randall Curtis J, Larson EB. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA. 2010;24:763–70.
40. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, Ely EW. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31:1226–34.
41. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304:1787–94.
42. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306–16.
43. Hopkins ROO, Weaver LKK, Pope D, ORME JFF, BIGLER EDD, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160:50–6.
44. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old the 90+ study. Ann Neurol. 2010;67:114–21.
45. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. Chest. 2006;130:869–78.
46. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171:340–7.
47. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GT, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104:21–6.

Functional Scores of Disability

Nathan E. Brummel

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_14

Learning Objectives

After reading this chapter, the learner will be able to:

- Understand terminology related to functional status, disability, and impairments.
- Understand major conceptual models of the disabling process.
- Understand common instruments to measure disability in ADLs and mobility.

14.1 Introduction

The ability to live independently is the most important factor in healthcare resource utilization and health-related quality of life [1]. Among community-dwelling older adults, the single largest risk factor for loss of independence (i.e., disability) is hospitalization, in particular those for a critical illness [2–7]. Sepsis, a common cause of critical illness, is now a leading cause of hospitalization among older adults in the United States [8]. The downstream costs of sepsis survivorship are considerable in light of the fact that up to 75% of older adults who survive a hospitalization for sepsis will develop long-lasting disability in one or more activities of daily living [8]. Because the incidence of sepsis increases with age, the aging of the world's population means a growing number of people will develop sepsis (and therefore be at risk for developing disability) in coming years [9–15].

Among survivors of critical illness, outcomes the burden of poor outcomes such as disability have come to light only within the last two decades [16–20]. Thus, while ongoing research seeks to describe, prevent, and treat this syndrome, those who care for patients affected by critical illness across the spectrum from acute illness to recovery need a deeper understanding of the processes which may result in disability and impaired function. In the ICU literature and in clinical practice, key terms related to function and disability are often used interchangeably. Moreover, conceptual models that can be used to understand better how disability develops and methods by which to assess disability may be unfamiliar to those caring for persons affected by critical illness. Therefore, this chapter will define important terminology related to function and disability, introduce major conceptual models of the disability process, and describe instruments that can be used to assess disability.

14.2 Terminology

Functional status, disability, and impairments are related terms that describe how a person performs in socially defined activities required to care for oneself. Confusion and misuse of these terms limit cross talk between those caring for persons with critical illness and survivors (e.g., ICU professionals, rehabilitation professionals, primary care providers) and slow research collaboration. This section, therefore, will define these terms and present a conceptual framework to understand better how these terms are used to describe a person's ability to perform the activities needed to live independently.

14.2.1 Functional Status

Functional status is an overarching term which refers to the activities that people do in the normal course of their lives to meet basic needs, fulfill usual roles, and maintain their health or well-being [21]. Though in common usage, functional status refers to one's physical functioning; in its broadest sense, functional status also incorporates the cognitive, psychological, social, and spiritual aspects of one's life.

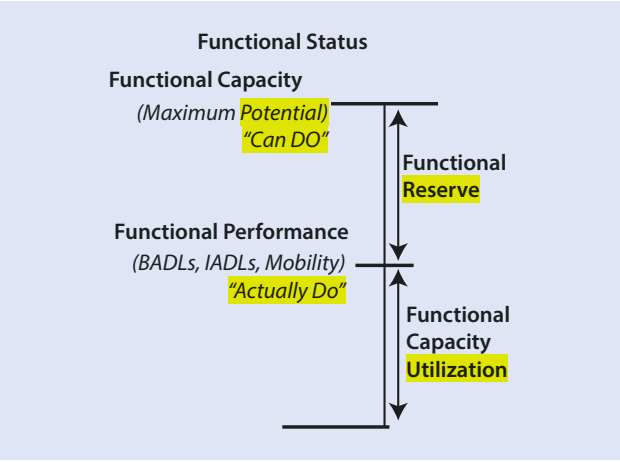


Fig. 14.1 Conceptual model of functional status. Functional status is an overarching term for what activities people do in the normal course of their lives to meet basic needs. Functional status is comprised of two components: functional capacity and functional performance. Functional capacity represents a person's maximum potential to perform an activity (top black horizontal line). Functional performance (middle black horizontal line) represents the actual level at which one functions to perform self-care activities such as basic and instrumental activities of daily living. When a person's functional performance is below a level at which he or she needs help to perform activities of daily living, disability can be considered to be present. (Adapted with permission from Leidy [21])

Functional status is comprised of four components: functional capacity, functional performance, functional reserve, and functional capacity utilization (Fig. 14.1) [21]. Functional capacity is a person's maximum potential to perform activities in any domain (e.g., physical, cognitive, psychological) [21]. Functional performance describes the activities people need and want to perform to meet their basic needs and to maintain their health and well-being [21]. In other words, functional capacity represents what one "can do," whereas functional performance represents what one "actually does" in his or her daily life. The next two components center on the exertion needed to perform those activities. Functional reserve is the difference between functional capacity and functional performance [21]. It represents the store of abilities that can be called upon when high levels of exertion are needed to accomplish a task. The inverse of functional reserve is functional capacity utilization. Functional capacity utilization is the proportion of one's functional capacity used to achieve a level of functional performance [21]. High levels of functional capacity utilization mean that high levels of exertion are required to perform the activities needed to meet one's basic needs (functional performance nears functional capacity, resulting in little functional reserve). This level of exertion may not be sustainable or the "cost" of exerting one's self becomes too high. Therefore, either by necessity or by choice, the performance of the activities required for independent living decreases or stops all together, resulting in disability.

14.2.2 Disability

Disability is a state of decreased functioning associated with a disease, disorder, injury, or other health conditions, which in the context on one's environment is experienced as a difficulty or dependency in performing the activities necessary to interact with one's envi-

Table 14.1 Activities of daily living can be categorized into basic ADLs (BADLs), instrumental (IADLs), and mobility activities. BADLs are those activities needed for basic physical self-care, IADLs are more complex tasks that allow one to interact with his or her environment, and mobility tasks are those necessary to move and travel. Examples of activies in each category are presented in the table

Basic activities of daily living	Instrumental activities of daily living	Mobility activities
Bathing	Use telephone	Move around home/apartment
Dressing	Shop	Walk ¼ mile (approx. 2–3 blocks)
Toileting	Housekeeping	Lift/carry 10 lbs.
Transferring	Laundry	Travel outside of home
Continence	Cook a meal	Travel outside of neighborhood
Eating	Manage medications	Travel outside of town
	Manage finances	
	Use transportation	

ronment within the context of one's socially defined role or roles [22]. In other words, disability represents the difference between the activities one is able to perform and the demands of a physical or social environment. At the most basic level, these are the activities required to live independently, and are classified as activities of daily living (ADLs). ADLs can be categorized hierarchically into basic ADLs (BADLs), instrumental ADLs (IADLs), and mobility activities (Table 14.1) [23].

Disability can be considered from both biomedical and social perspectives. A biomedical view of disability considers the disruptions of the structure or function of body systems that lead to disability. The social view of disability considers the social, environmental, and personal factors leading to disability. Thus, these complementary views of disability can be used to understand better disabilites after critical illness and have implications for rehabilitaiton strategies.

14

14.2.3 Impairments

Impairments are anatomical, physiological, mental/cognitive, or emotional abnormalities or problems in specific body structures or functions [24–27]. Impairments can reduce physical, mental, or social functioning, therefore affecting one's performance of ADLs and/or mobility activities. In other words, severe impairments can result in disability.

14.2.4 Linking Functional Status, Disability, and Impairments

Because functional performance describes the actual activities one does, it is this component of functional status that defines disability. Thus, following a critical illness if one's functional performance remains high enough, he or she is able to perform ADLs without

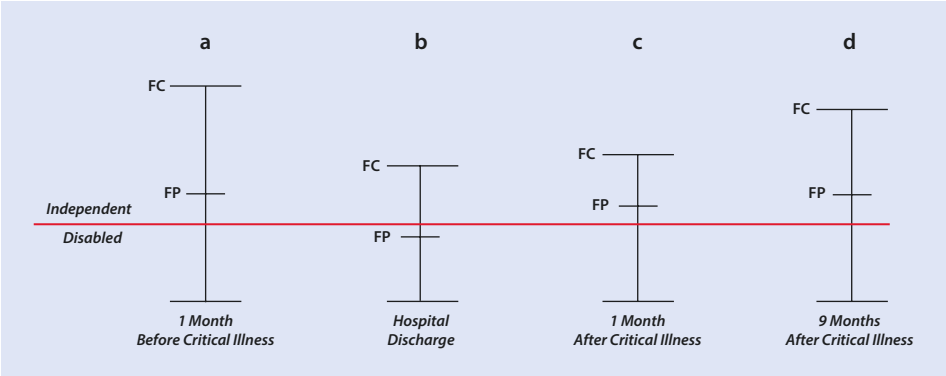


Fig. 14.2 Functional status and critical illness. This figure illustrates changes in functional status for a hypothetical patient with sepsis during a critical illness and recovery. Panel **a** shows functional status before critical illness. Panels **b**, **c**, and **d** show changes to functional status at hospital discharge, 1 month after discharge, and 9 months after discharge, respectively. See text for illustrative example

help from another. When an illness or injury results in a severe impairment, however, functional performance may decline. If functional performance declines below the level at which a person is able to perform ADLs without assistance, disability is present.

To illustrate how the components of functional status are affected by critical illness, consider the case of a 62-year-old woman who develops influenza pneumonia with resultant acute respiratory failure requiring 5 days of mechanical ventilation and 2 days of septic shock. Prior to her illness, she lived independently with her husband, worked as a partner at a law firm, and was physically active playing in a tennis league two nights per week. Her baseline functional status is depicted in Fig. 14.2, panel a. Her critical illness was complicated by the development of severe ICU-acquired weakness preventing her from being able to bathe, transfer out of her bed, or ambulate to the restroom without the help of another person. As a result of this impairment in her neuromuscular function, her functional capacity and functional performance have declined to the point where she has become disabled in two BADLs and in mobility (Fig. 14.2, panel b). Because of her disability, she is discharged to an inpatient rehabilitation facility. She sees you in the ICU recovery clinic after 1 month of inpatient rehabilitation. She is now able to perform all her BADLs and IADLs without help. She is also able to walk short distances without help, but is unable to walk distances more than 10 meters because of fatigue. She states her day-to-day activities also cause significant fatigue and she feels "worn down" (Fig. 14.2, panel c). Note the improvement in her functional performance since discharge, but the persistent decrease in her functional capacity compared with her baseline. Because of the increased proportion of her functional capacity required to achieve her functional performance level (i.e., functional capacity utilization is increased), she is experiencing symptoms of fatigue while performing her ADLs. You recommend that she resume a progressive exercise program of daily walking in an attempt to increase her functional capacity. At her visit with you 9 months after hospital discharge, she reports to you that she is now able to walk 5–6 days per week for 30 minutes. She no longer feels fatigued performing her day-to-day activities, though she is unable to play tennis. Figure 14.2, panel d, demonstrates a large increase in functional capacity with some improvement in her functional performance. Thus, her functional capacity utilization has decreased and the exertion required to perform her ADLs is less and her symptoms of fatigue are improved.

14.3 Models of the Disability Process

With an understanding of terminology related to function, disability, and impairments, we now shift our focus to understanding why and how disability can develop through the use of three models: the vulnerability hypothesis, the Nagi model of the disability process, and the International Classification of Function (ICF) model.

Why some persons affected by critical illness become disabled afterward while others do not can be understood through the vulnerability hypothesis (Fig. 14.3). Proposed initially to explain the development of delirium in acutely ill persons [28], the vulnerability hypothesis has been applied widely to explain other syndromes of aging, such as disability [3, 7, 29]. The vulnerability hypothesis states that disability develops as a function of an acute stressor encountered by a vulnerable host [29]. As described in the introduction, hospitalization, particularly for a critical illness, is far and away the strongest risk factor for the development of reduced functional performance resulting in disability in older adults [7]. While critical illness is a strong predictor of disability, those caring for persons with critical illness recognize that critical illness is not a homogenous event. Thus, even among persons who are critically ill, factors such as the number and type of organ failures, the duration of critical illness, and iatrogenic factors (e.g., immobility, sedation) will affect the intensity of a critical illness. What may be less familiar are the factors that increase vulnerability to the development of disability. In clinical practice, increased vulnerability to poor outcomes can be recognized as frailty. Frailty is a syndrome that is characterized by the loss of physiological reserve across multiple organ systems that reduces one's ability to maintain or to restore homeostasis in the setting of an acute stressor [30]. Two recent cohort studies have found after considering a number of factors such as age and the number of comorbidities that more severe frailty is independently associated with disability after critical illness [31, 32]. Moreover, while considered to be a classic syndrome

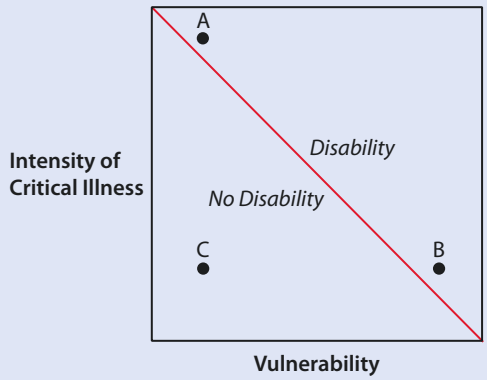


Fig. 14.3 The vulnerability hypothesis. The vulnerability hypothesis states that disability develops as a function of the intensity of a critical illness (y-axis) and a patient's underlying vulnerability (x-axis). The diagnoal line shows the division between disability and no disability. Point A shows a person with low vulnerability who suffered a high-intensity critical illness and develops disability. Point B shows a person with high vulnerability who suffered a low-intensity critical illness and develops disability. Point C shows a person with low vulnerability who develops a low-intensity critical illness and does not develop disability. See text for illustrative example. (Adapted with permission from Gill [29])

of aging, frailty was present in substantial numbers of persons in the 30s, 40s, and 50s, indicating that increased vulnerability is present in among persons of all ages admitted to intensive care units [32, 33].

To place the vulnerability hypothesis into clinical context, let us revisit the example of our 62-year-old woman with influenza pneumonia. Prior to her illness, she was quite fit, working in a cognitively demanding job, and was playing in a tennis league and therefore had very low pre-illness vulnerability. Despite this low underlying vulnerability, she developed disability as a result of her intense episode of critical illness (Fig. 14.3, point A). Contrast her case with that of a second patient. An 87-year-old man with metastatic lung cancer, coronary artery disease, and mild cognitive impairment, who has difficulty walking at baseline, develops septic shock for 2 days secondary to a urinary tract infection (Fig. 14.3, point B). He is hospitalized for 5 days and at the time of hospital discharge is unable to bathe himself or to walk to the restroom. Because of his BADL disabilities, he is discharged to inpatient rehabilitation. Despite having a low-intensity critical illness relative to our first patient, he became disabled as a result of his greater underlying vulnerability. If our 62-year-old woman from the first case, who had low underlying vulnerability, developed the same intensity critical illness that our highly vulnerable patient had, she would not have developed disability (Fig. 14.3, point C). Thus, it is the combination of intensity of critical illness and underlying vulnerability that can explain why disability develops in some people, but not others.

While the vulnerability hypothesis is helpful to understand why certain persons may develop disability, it does not help to understand *how* disability develops after critical illness. Two complementary models, the Nagi model and the International Classification of Function (ICF) model, can be used to link processess present during critical illness and recovery with disability.

The Nagi model, originally proposed in the 1960s and modified by Verbrugge and Jette in the mid-1990s, considers disability from a biomedical perspective [24, 25, 34]. Simply put, the model states that diseases or injuries disrupt normal physiologic functions (pathology) to result in dysfunction or structural abnormalities in body system(s) (impairments) that cause restrictions in the performance of physical or mental activities (functional limitations) which when placed into a specific context prevent the performance of socially defined roles and tasks (disability) (Fig. 14.4a).

First proposed in 2001, the WHO ICF model incorporates both the biomedical and social perspectives of disability [26]. The ICF model posits that disability arises out of an interaction between a health condition, human factors (i.e., body functions and structures, carrying out tasks or activities, participation in life situations), and contextual factors (i.e., personal factors and environmental factors) (Fig. 14.4b).

While the approach to the disabling process differs somewhat between these two models, both have utility in understanding the disability process after critical illness, depending on the context within which one is evaluating disability. For example, for a clinical researcher focused on studying the biological mechanisms by which sepsis may result in muscle weakness and wasting leading to disability in BADLs, the Nagi model may be the most informative because of its focus on how a specific pathology can result in disability. In contrast, the ICF model, with its focus on social factors such as a person's physical living environment, his or her social support, coping strategies, and governmental policies toward those with disabilities, would be more informative to a researcher studying the potential association between health care disparities and prolonged disabilty after sepsis.

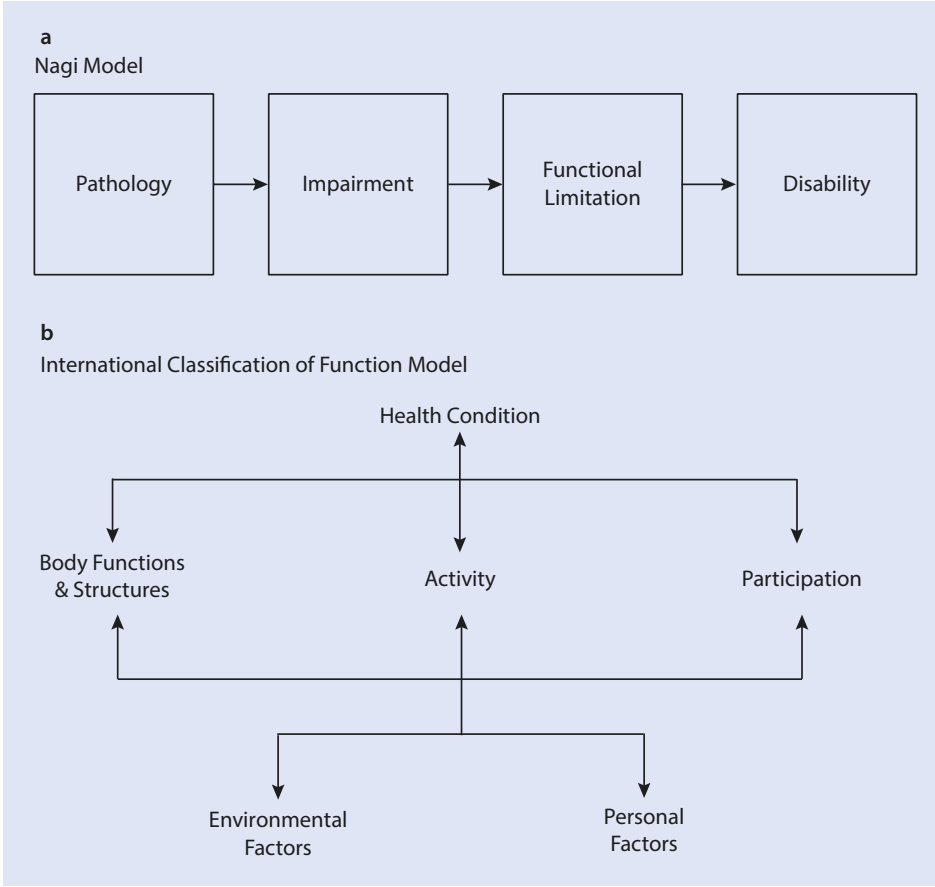


Fig. 14.4 Conceptual models of the disability process. Panel **a** presents the Nagi model and panel **b** presents the World Health Organization International Classification of Function model. See text for descriptions of these models. (Adapted with permission from Verbrugge and Jette [34])

14

14.4 Assessing Functional Performance in BADLs, IADLs, and Mobility

A number of instruments exist to measure functional performance of ADLs, IADLs, and mobility [35–41]. These instruments vary with regard to the type (e.g., questionnaire vs. performance-based), time needed to complete the instrument, activities assessed, and training required. Thus, the choice of an instrument will depend on factors such as the context of the assessment (e.g., clinical versus research) and the level of detail about a person's functional performance desired from that assessment (e.g., general assessment versus detailed measure of levels of performance across multiple domains of activity). For example, in a busy clinical ICU setting where a clinician is seeking to determine a patient's baseline level of performance, a quick disability assessment that asks the patient or family members about the need for help or difficulty in bathing, dressing, transferring, and getting around may be sufficient. In contrast, in the context of a research study, evaluating the effect of an intervention on performance of ADLs where measurement of small, and

Table 14.2 Common intruments used to measure Functional Performance in BADLs, IADLs, and Mobility in critical illness and recovery

Instrument	Domain assessed	Type of instrument	Items	Time required (minutes)	Comments
Clinical history	BADLs/ mobility	Clinical history	8	1–2	Quick; few details about specific help needed to complete activities
Katz Index of ADL [35]	BADLs	Questionnaire	6	2–3	Quick; graded assessment of help needed to complete BADLs
Barthel Index [36]	BADLs	Questionnaire	10	2–3	Quick; limited to "independent" vs. "with help"
Lawton-Brody Index [37]	IADLs	Questionnaire	8	2–3	Quick; graded assessment of help needed to complete IADLs
FAQ [38]	IADLs	Questionnaire	10	2–3	Quick; graded assessment of help needed to complete IADLs
Life-Space Assessment [39]	Mobility	Questionnaire	15	5	Spectrum of mobility activities assessed
WHO-DAS 2.0 [40]	BADLs, IADLs, mobility, cognition, social interaction	Questionnaire	36	10	Broad assessment of multiple domains of function; less detail of function in specific domains
FIM [41]	BADLs, cognition	Performance	16	30–45	Long; detailed assessment of actual performance; training required to perform assessments

BADLs basic activities of daily living, *IADLs* instrumental activities of daily living, *FAQ* Functional Activities Questionnaire, *WHO-DAS II* World Health Organization Disability Assessment Schedule 2.0, *FIM* Functional Independence Measure

potentially meaningful, improvements in functional performance may use a more detailed assessment, such as observation of a patient performing ADLs, may be needed. Table 14.2 compares some common instruments used to measure performance of BADLs, IADLs, and mobility in persons with critical illness across the spectrum from acute illness to recovery.

14.5 Recovery from Disability

Despite often being thought of as a progressive or permanent condition, disability following acute and critical illness is a dynamic condition characterized by high rates of recovery [42]. Data from the Precipitating Events Project (PEP), a longitudinal study that performed monthly assessments of disability from 754 community-dwelling older adults over more than a decade, show that 80% those who developed disability after a hospitalization for an acute or critical illness recovered within 1 year [42]. Though lower than patients with acute illness, 52% of those hospitalized for a critical illness recovered [43]. Of those patients who developed a disability, but who recovered, most maintained independent functional performance for 6 months or longer. Thus, the majority of patients who become disabled following hospitalization for an acute or critical illness will recover from their hospital-associated disabilities.

Several important factors, however, affect the chances of recovery among those who develop disability following a hospitalization. First, severity of illness reduced the proportion of patients who recovered. In PEP, among those participants whose hospitalization included an ICU stay, the proportion of patients who recovered to their pre-illness functional performance was nearly 30% lower [43]. Second, the duration of the disability episode affects recovery. Among those whose disability episode persisted for greater than 2 months after discharge, only 70% recovered to independence by 1 year, 10% lower than the overall cohort [2]. Third, even though the majority of patients recover at 1 year and shorter episodes increase the chances of recovery, over time, even short episodes of disability are associated with the development of future disability [44]. Finally, the presence of sensory impairment (e.g., vision or hearing loss) is associated with lower probability of recovery whereas higher body mass index and greater confidence in performing physical tasks (e.g., physical self-efficacy) are associated with greater probability of recovery [43].

Conclusion

The ability to live independently depends on the ability to perform basic self-care activities. Functional status, disability, and impairments represent distinct (but interrelated) concepts related to ability to live independently. Because the development of disability after critical illness is complex and not well understood, complementary models of the disability process can be used as a framework to guide research and interventions. How best to measure performance of ADLs and mobility should be guided by the purpose of the assessment and detail of information needed.

Take-Home Message

The development of disability after critical illness is a complex process that is not well understood. Improving use of terminology and an understanding of the major conceptual models of the disability process by those of care for persons with critical illness are important first steps in reducing this component of post-critical illness suffering.

References

1. Ferrucci L, Baldasseroni S, Bandinelli S, de Alfieri W, Cartei A, Calvani D, et al. Disease severity and health-related quality of life across different chronic conditions. J Am Geriatr Soc. 2000;48(11):1490–5.
2. Gill TM, Allore HG, Holford TR, Guo Z. Hospitalization, restricted activity, and the development of disability among older persons. JAMA. 2004;292(17):2115–24.
3. Gill TM, Gahbauer EA, Murphy TE, Han L, Allore HG. Risk factors and precipitants of long-term disability in community mobility: a cohort study of older persons. Ann Intern Med. 2012;156(2):131–40.
4. Brown CJ, Roth DL, Allman RM, Sawyer P, Ritchie CS, Roseman JM. Trajectories of life-space mobility after hospitalization. Ann Intern Med. 2009;150(6):372–8.
5. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. Am J Respir Crit Care Med. 2011;183(8):1037–42.
6. Ehlenbach WJ, Larson EB, Curtis JR, Hough CL. Physical function and disability after acute care and critical illness hospitalizations in a prospective cohort of older adults. J Am Geriatr Soc. 2015;63(10):2061–9.
7. Gill TM, Allore HG, Gahbauer EA, Murphy TE. Change in disability after hospitalization or restricted activity in older persons. JAMA. 2010;304(17):1919–28.
8. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc. 2012;60(6):1070–7.
9. Ortman J, Velkoff V, Hogan H. An aging nation: the older population in the United States. Washington, D.C.: United States Census Bureau; 2014.
10. Sjoding MW, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Longitudinal changes in ICU admissions among elderly patients in the United States. Crit Care Med. 2016;44(7):1353–60.
11. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006;34(1):15–21.
12. Needham DM, Bronskill SE, Sibbald WJ, Pronovost PJ, Laupacis A. Mechanical ventilation in Ontario, 1992–2000: incidence, survival, and hospital bed utilization of noncardiac surgery adult patients. Crit Care Med. 2004;32(7):1504–9.
13. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr, Committee on Manpower for P, et al. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? JAMA. 2000;284(21):2762–70.
14. Carson SS, Cox CE, Holmes GM, Howard A, Carey TS. The changing epidemiology of mechanical ventilation: a population-based study. J Intensive Care Med. 2006;21(3):173–82.
15. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet. 2010;376(9749):1339–46.
16. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683–93.
17. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
18. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42(4):849–59.
19. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference*. Crit Care Med. 2012;40(2):502–9.
20. Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, et al. Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit Care Med. 2014;42(12):2518–26.
21. Leidy NK. Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. Nurs Res. 1994;43(4):196–202.
22. Leonardi M, Bickenbach J, Ustun TB, Kostanjsek N, Chatterji S, Consortium M. The definition of disability: what is in a name? Lancet. 2006;368(9543):1219–21.
23. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31(12):721–7.
24. Nagi SZ. A study in the evaluation of disability and rehabilitation potential: concepts, methods, and procedures. Am J Public Health Nations Health. 1964;54:1568–79.

25. WHO. International classification of impairments, disabilities and handicaps. Geneva: World Health Organization; 1980.
26. World Health Organization T. Towards a common language for functioning, disability, and health. Geneva: World Health Organization; 2002.
27. Jette AM. Toward a common language for function, disability, and health. Phys Ther. 2006;86(5):726–34.
28. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999;10(5):393–400.
29. Gill TM. Disentangling the disabling process: insights from the precipitating events project. Gerontologist. 2014;54(4):533–49.
30. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.
31. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ. 2014;186(2):E95–E102.
32. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, et al. Frailty and subsequent disability and mortality among patients with critical illness. Am J Respir Crit Care Med. 2017;196(1):64–72.
33. Bagshaw M, Majumdar SR, Rolfson DB, Ibrahim Q, McDermid RC, Stelfox HT. A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care. 2016;20(1):175.
34. Verbrugge LM, Jette AM. The disablement process. Soc Sci Med. 1994;38(1):1–14.
35. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA. 1963;185:914–9.
36. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61–5.
37. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179–86.
38. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982;37(3):323–9.
39. Peel C, Sawyer Baker P, Roth DL, Brown CJ, Brodner EV, Allman RM. Assessing mobility in older adults: the UAB study of aging life-space assessment. Phys Ther. 2005;85(10):1008–119.
40. Ustun TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, et al. Developing the World Health Organization disability assessment schedule 2.0. Bull World Health Organ. 2010;88(11):815–23.
41. Dodds TA, Martin DP, Stolov WC, Deyo RA. A validation of the functional independence measurement and its performance among rehabilitation inpatients. Arch Phys Med Rehabil. 1993;74(5):531–6.
42. Hardy SE, Gill TM. Recovery from disability among community-dwelling older persons. JAMA. 2004;291(13):1596–602.
43. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors associated with functional recovery among older intensive care unit survivors. Am J Respir Crit Care Med. 2016;194(3):299–307.
44. Gill TM, Kurland BF. Prognostic effect of prior disability episodes among nondisabled community-living older persons. Am J Epidemiol. 2003;158(11):1090–6.

Pain, Analgesic Effectiveness, and Long-Term Opioid Dependency

Yoanna Skrobik and Pamela Flood

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_15

Learning Objectives

- Understand the content and limitations of current evidence in providing effective analgesia to adult ICU patients.
- Appreciate the limitations and potential side effects of opiate use in the critically ill.
- Recognize the risks for opiate withdrawal and dependency after exposure in the ICU.

15.1 Introduction

Routine pain assessment and the procurement of effective analgesics are of paramount importance to critical care patients. Constant evaluation underpins the important balance between pain relief and the pharmacological side effects of administered agents. The significance of these issues was highlighted during the production of the most recent Society of Critical Medicine's (SCCM) Pain, Agitation, Delirium, Immobility, and Sleep (PADIS) Guidelines [1]. Patients who partnered as authors and contributors in the SCCM PADIS effort ranked this dimension of clinical care as *essential* to their well-being, leading to its prioritization for these guidelines [2].

Opioids restrictions in the intensive care unit (ICU) setting, and in the hospital, because of fears related to the opioid epidemic, led many International Pain Summit worldwide delegates to produce the "Declaration of Montreal" [3]. This position paper advocates considering pain management as a basic human right and pain assessment and symptom-based management as a fundamental health-care professional obligation.

In this chapter, pain assessment and evidence to support its safe and effective management in the ICU setting will be addressed. Data addressing the risks of opiate exposure in critical care will also be reviewed.

15.2 Pain Assessment in ICU Practice

Routine pain assessments are mandated by most hospital accreditation processes and are assumed to be part of providing critical care [4]. The current [1] and previous [5] SCCM guidelines recommend routinely asking patients to score their pain intensity if they are able to do so. In patients whose illness or sedation precludes pain assessments using a reliable verbal or written scale, tools to assess behavioral pain indicators have been validated in the ICU environment [6, 7].

Pain is frequent in the critically ill [8], occurs in up to 50% of medical and surgical patients at rest [9], and can increase to over 80% during common care procedures [9]. Procedural interventions in the ICU cause both pain and emotional distress [10]. Anticipating this distress and having insufficient analgesia heighten pain severity [11]. Survivors of critical illness have corroborated this concern and focused on pain assessment and management as a top priority during the PADIS guidelines [1].

The data on how pain is measured and managed in the critically ill suggest there is considerable room for improvement. A recent survey of all Dutch adult critical care units reported that among nurses, 36% believed nursing opinion about pain severity trumped the patient's self-report, even in clinical contexts where pain scales were routinely used and recorded [12]. Despite solid evidence that a reproducible behavioral pain scale remains the best metric to evaluate pain in patients unable to communicate their pain severity directly

[13–16], Dutch nurses overwhelmingly (98%) judged themselves to be more accurate than any such tool [12]. Similarly, a substantial proportion of Canadian ICU nurses did not use pain assessment tools for patients who were unable to communicate and were unaware of the pain management guidelines advocating their use in published professional society "best practices" [17]. Routine communication during bedside rounds as to whether analgesia was adequate occurred 61% of the time. Adjusting analgesics based on the patient's pain score, another tenet of pain management quality, was even less frequent (42%) in this study [17]. Evidence does not appear to drive either overall nursing practice [18] or the provision of adequate analgesia. Documentation of the underestimation of pain by critical care nurses, and failure to administer analgesics despite their patient's discomfort, contrasts with the commitment they express wishing to provide to ensure pain relief. The delineation of the mechanism of this paradox and recommendation of a pathway to its resolution are explored in very few studies and remain unaddressed in most of those, cited above, that demonstrate its existence. A recent review suggests that beliefs (concerning opioids, gender, culture, and subjective norms), rather than knowledge and data, significantly drive nurses' pain management-related behaviour. One publication proposes belief-altering interventions as a focus for interventions that may better improve the observed knowledge-to-action gaps [19].

15.3 Support for Pain Assessment and Symptom-Based Adjustment Literature in the Critically Ill

Of all the clinical dimensions related to pain and its management in critical illness, none are as well described as those pertaining to routine pain assessments and adjusting analgesic interventions accordingly. Tallying pain and adjusting medications to patient needs ensure pain relief, reduce the likelihood of lasting traumatic memories [16], and shorten the duration of mechanical ventilation and ICU length of stay [20, 21]. In addition, it reduces costs [22] and opiate exposure [21]. As discussed above, pain can readily be evaluated using validated tools in the majority of critically ill adults, including delirious patients who are unable to self-report [23].

15.4 Pharmacologic Management Overview

Guidelines providing an overview of non-pharmacological and pharmacological analgesic management in critically ill adults were recently published [1]. A summary of the current relevant ICU pharmacological literature, general comments about guideline recommendations, as well as important "unknowns" will be summarized here.

The 2018 SCCM PADIS guideline questions were based on patient-partner rank-ordering priorities from an item list generated by expert panel members [2] based on clinical relevance. Analgesia and its management included non-pharmacological, multimodal analgesia, and opiate-based interventions. Evidence synthesis and recommendations were based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [24]. The GRADE method's reliability, reproducibility, and limitations were untested until recently [25] when a guideline panel of GRADE-trained experts prospectively validated these features [26]. In six (of nine) GRADE domains, expert concordance could, at best, be considered fair [26]. This caveat, the dearth of publications

addressing adult ICU pain management, and the unaddressed challenge of nursing beliefs limit translating the content of these guidelines to bedside practice.

15.5 Opiates

The most recent SCCM effort limited its description of opiate use for analgesic purposes to procedural pain management [1]. The 2013 guidelines, however, recommended this drug class as the primary analgesic for non-neuropathic pain in the ICU [5] on the premise based on acute pain literature that they are effective.

Continuously infused opiates are the most commonly administered analgesic to the vast majority of critically ill adults [27–31]. However, no prospective or comparative studies evaluate their effectiveness and comparative safety during or after critical illness. The 2013 guidelines highlighted pharmacologic characteristics of readily available molecules [32] and cited two ICU studies. One trial evaluated 152 mostly (95%) postoperative patients who were treated with fentanyl or remifentanil until extubation with a 24-hour follow-up [33]. The second compared remifentanil, fentanyl, and morphine infusions in 161 neuro-critically ill patients [34]. Although neither study focused on adequate analgesia as an end point, there were no significant differences in reported pain scores between the opiate regimens. Accordingly, the authors pointed out that "High-quality study data are scarce in support of using one opiate over another in ICU patients."

How frequent opiate administration in adult ICU contrasts with how weak the data are to support their analgesic efficacy in the critically ill and the dearth of safety data reporting well-established opiate side effects (constipation, excessive sedation, tolerance, and psychological effects). One study compared non-protocolized patient management with a protocol specifically precluding opiate administration without documenting the presence of pain above pre-established pain thresholds. In this population (nearly half were surgical ICU patients), 36% never required opioids. Pain scores improved, while opioid administration was reduced by 80% in comparison to the non-protocolized group [21].

Administering opiates continuously may counter the intent to procure effective analgesia. Opiate tolerance occurs most predictably with continuous exposure to high-dose high-potency opioids [35]. The risk is highest when unadjusted opiate administration accompanies inadequate pain scale titration and de-escalation of narcotics.

15

Mu receptors are believed to mediate opioid analgesic effect. With continuous or repetitive opiate exposure, mu-opioid receptor-mediated changes associated with opiate tolerance [36] occur through alterations in the expression of the cell surface receptor and/or transcription-related downstream regulation [35]. This feature also occurs in delta opiate receptors. Animal models evaluating delta receptor downregulation suggest that diminished receptor sensitivity and transcriptional and post-translational changes may occur after as little as 48 hours and predictably take place within 7 days of agonist receptor exposure [37].

Whether mu receptors behave using similar mechanism is unclear [38]. Mu- and delta-opioid receptors are co-expressed in a many small neurons in the dorsal root ganglion. Their expression in nociceptive afferents is enhanced by stimulus-induced cell-surface expression of δ-opioid receptors and contributes to morphine tolerance [39].

Opiate tolerance is believed to result primarily from receptor desensitization and upregulation of the cAMP pathway; many other biological and pharmacological and

genetic clinical features may also contribute to what translates into ineffective analgesic effect of opioids [40]. Gender and other interindividual variability also influence analgesic effectiveness. "Standard" opiate doses may not account for individual patient features such as sex differences in pain perception [41] and opiate efficacy [42]. In addition, pharmacokinetic features (volume of distribution, drug accumulation [32], the effect of critical illness on clearance, and drug-drug interactions [43]) can influence opiate effectiveness and the incidence of adverse drug events in critically ill adults.

Numerous biological changes accompany opiate exposure, which substitutes morphine or morphine-like molecules to the brain's natural ligand endorphins, beta endorphins, and dynorphins. Opiate molecules binding to their receptors not only impact analgesia but also mood and immunity [38]. Descriptions of interindividual receptor characteristic and biological variability have challenged "single model" constructs [36]. The recent discovery of mu, kappa, and delta genetic variability [44] has led to a better biological understanding of the opiate receptor's complex three-dimensional structure and of the modulatory interplay between intrinsic or extrinsic ligands and the number of potential stimulated sites. Basic research investigators are shedding unprecedented light on the relationship between biology, effective analgesia, and addiction "gateways" [36, 45]. Although these opiate receptor-related findings may not be ripe for bench-to-bedside translation, their identification provides another compelling argument for assessing and managing pain and using opioids on an individualized and "as-needed" basis.

Moreover, in the perioperative setting, intraoperative administration of high doses of opioids increases postoperative opioid requirements and worsens pain scores through a mechanism thought to be due to acute tolerance and/or perioperative *opioid*-induced hyperalgesia (OIH) [46]. Remifentanil infusion is commonly used in the ICU and in the intraoperative setting. Remifentanil infusion rates of above 0.25 μg kg^{-1} min^{-1} are associated with higher postoperative opioid consumption, suggesting tolerance infusion rates greater than 0.2 μg kg^{-1} min^{-1} are characterized by lower experimental pain thresholds that point to OIH [47].

Opioid-induced hyperalgesia is generally thought to result from neuroplastic changes in the peripheral and central nervous system (CNS) that lead to sensitization of pronociceptive pathways allodynia and waning efficacy or previously effective opioid management. There are many proposed molecular mechanisms that underlie OIH, but the majority implicate the N-methyl-D-aspartate (NMDA) receptor. Treatment supplementation with NMDA receptor modulators reduces the reliance on opioid analgesia [48]. Whether this complicates analgesia in the critically ill has not been studied.

15.6 Multimodal Analgesia (Co-analgesia)

The paucity of literature addressing pharmacological co-analgesic agent use and its efficacy and safety in critical illness contrasts with how commonly these agents are used [28]. The sparse literature that exists reports the safety and efficacy of single pharmacological interventions; it is unsurprising that no publications report as to the effectiveness and/or risks of analgesic combinations in the ICU. However, there is substantial evidence in other settings for synergy between many analgesic classes that could be useful in limiting the dose-limiting side effects of any single agent [49–52]. These concepts underlie the WHO pain ladder [53].

Considering the general safety concerns associated with opioid use (sedation, delirium, respiratory depression, ileus, and immunosuppression), the SCCM PADIS panel evaluated multimodal interventions aiming to minimize opiate administration while ensuring adequate pain control. The SCCM PADIS pain section panel thus reviewed acetaminophen, non-steroidal anti-inflammatory agents, ketamine, intravenous lidocaine, nefopam, and (grouped) agents commonly used for neuropathic pain (gabapentin, carbamazepine, and pregabalin). The available literature and their recommendations for each molecule are described below.

Acetaminophen: Two studies (113 cardiac surgery and 40 abdominal surgery patients) evaluated acetaminophen and recommended its administration to decrease pain intensity and minimize opiate exposure [1]. A recent editorial pointed out these ICU-based data are insufficient to support this recommendation [54] as "data for reduced opioid requirements, improved analgesia and reduced analgesia-related adverse events appear to be lacking within the critical care literature." Benefits outside the ICU, acetaminophen's ubiquitous administration [55], and its reputation for safety were considered. However, common conditions in critical illness including liver and kidney dysfunction may limit this molecule's safety, particularly in the perioperative setting where it is most commonly administered.

Ketamine: One single-center study, and two non-ICU publications, supported the panel "suggest(ing) low-dose ketamine as an adjunct to opioid therapy when seeking to reduce opioid consumption in post-surgical adults admitted to the ICU." A subsequent larger study, published after the guidelines, contradicts ketamine's usefulness in minimizing opiate exposure [56]. Whether the molecule may help OIH management is unclear in the critically ill.

Lidocaine was described in a single cardiac surgery study where 50/100 randomized patients had no analgesic benefit [1]. Non-ICU data suggesting lidocaine may be useful in postoperative abdominal surgery pain notwithstanding the suggestion was to "not routinely use IV lidocaine as an adjunct to opioid therapy for pain management in critically ill adults." The risk versus benefit may vary interindividually, considering that of renal function impacts lidocaine clearance directly.

The panel also recommended not using *non-steroidal anti-inflammatory medications* based on two small (abdominal and cardiac surgery) studies, given minimal benefit and perception of risk related to drug-induced renal function or worsening or pre-existing renal dysfunction. These complications are not clearly associated with this drug class in adult ICU patients and are beneficial in pediatric ICU patients [57].

Anti-neuropathic analgesic evaluation was based on four studies, two in Guillain-Barré patients (gabapentin, and gabapentin vs. carbamazepine vs. placebo) and two in cardiac surgery patients (pregabalin). A recommendation and a suggestion supported this molecule class' administration in neuropathic and post-cardiac surgery pain, respectively.

Finally, *nefopam* was recommended with the caveat of its limited availability in North America.

Dexmedetomidine is an alpha-adrenergic antagonist with a safer hemodynamic profile in the critically ill. Its role as a potential multimodal co-analgesic was not retained as a priority topic in the PADIs guidelines, despite the number of studies suggesting its administration is associated with a significant improvement in pain scores and reduction in opiate requirements [58–61].

This summary highlights the impressive absence of data on opioid and non-opioid analgesic effectiveness and safety in the critical care setting. Recent biologic and pharma-

cokinetic research suggests significant complexity underlying variability in, and consequences of, opiate analgesia. In the ICU, analgesics, specifically opioids, are usually prescribed in fixed doses rather than in incremental and (importantly) decremental adjusted doses. This practice profile suggests a knowledge gap that was not addressed in the recent guidelines [1].

The SCCM PADIS critical care guideline recommendations integrated non-pharmacological management. Music and massage [62] were noted to help pain management and serve to highlight that holistic approaches improve pain management [1] and should be integrated into the overall care plan.

Long-term outcomes related to pain management and its efficacy remain undescribed in the critically ill. Although posttraumatic stress disorder (PTSD) has been attributed to painful memories of ICU pain in a few studies [63–65], it is not known whether inadequate pain relief during critical illness predicts long-term effects such as chronic pain.

Administering opiates in pediatric ICU patients has long been equated with withdrawal symptoms, although symptom-driven scales do not distinguish between sedative and opiate withdrawal [66]. Indeed, pediatric patients are routinely screening for iatrogenic withdrawal if they have received opiates for 72 hours or longer. Only two published address opiates as a drug class [31, 66, 67] and suggest that withdrawal occurs in 15–55% of ICU patients. No opiate withdrawal scale has ever been validated in adults. Finally, do we cause opiate addiction with the high doses of continuous opioids we prescribe? The small quantity of data available suggests not [68]. In this single-center 5-year retrospective review, opiate infusions during critical illness did not predict opiate prescription at discharge [68]. However, the consequences with longer follow-up and among a population known to be at risk should be evaluated with long-term quality assurance programs.

Conclusion and Take-Home Message

The critical care community faces considerable challenges in ensuring that patients get assessed for pain and that these assessments guide therapy. Several gaps have been identified:

- Assuring that evidence-based guidelines are followed for assessment and assessment-guided treatment
- Establishing which pharmacological approach(es) are most effective in which population
- Better understanding of the mechanistic pathways underlying opiate effectiveness and adverse drug reactions
- Which assessments and therapeutic choices are most patient-centered
- Addressing long-term benefits and outcomes of various analgesic paradigms

References

1. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–e73.
2. Devlin JW, Skrobik Y, Rochwerg B, Nunnally ME, Needham DM, Gelinas C, et al. Methodologic innovation in creating clinical practice guidelines: insights from the 2018 society of critical care medicine pain, agitation/sedation, delirium, immobility, and sleep disruption guideline effort. Crit Care Med. 2018;46(9):1457–63.
3. Cousins MJ, Lynch ME. The Declaration Montreal: access to pain management is a fundamental human right. Pain. 2011;152(12):2673–4.
4. Potera C. Joint commission reassesses pain management. Am J Nurs. 2017;117(11):13.

5. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
6. Kotfis K, Strzelbicka M, Zegan-Baranska M, Safranow K, Brykczynski M, Zukowski M, et al. Validation of the behavioral pain scale to assess pain intensity in adult, intubated postcardiac surgery patients: a cohort observational study – POL-BPS. Medicine. 2018;97(38):e12443.
7. Chanques G, Pohlman A, Kress JP, Molinari N, de Jong A, Jaber S, et al. Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report. Crit Care. 2014;18(5):R160.
8. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology. 2007;107(5):858–60.
9. Puntillo KA, Morris AB, Thompson CL, Stanik-Hutt J, White CA, Wild LR. Pain behaviors observed during six common procedures: results from thunder project II. Crit Care Med. 2004;32(2):421–7.
10. Puntillo KA, Max A, Timsit JF, Ruckly S, Chanques G, Robleda G, et al. Pain distress: the negative emotion associated with procedures in ICU patients. Intensive Care Med. 2018;44(9):1493–501.
11. Puntillo KA, Max A, Timsit JF, Vignoud L, Chanques G, Robleda G, et al. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. Am J Respir Crit Care Med. 2014;189(1):39–47.
12. van der Woude MC, Bormans L, Hofhuis JG, Spronk PE. Current use of pain scores in Dutch intensive care units: a postal survey in the Netherlands. Anesth Analg. 2016;122(2):456–61.
13. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–63.
14. Aissaoui Y, Zeggwagh AA, Zekraoui A, Abidi K, Abouqal R. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. Anesth Analg. 2005;101(5):1470–6.
15. Cade CH. Clinical tools for the assessment of pain in sedated critically ill adults. Nurs Crit Care. 2008;13(6):288–97.
16. Topolovec-Vranic J, Canzian S, Innis J, Pollmann-Mudryj MA, McFarlan AW, Baker AJ. Patient satisfaction and documentation of pain assessments and management after implementing the adult nonverbal pain scale. Am J Crit Care. 2010;19(4):345–54; quiz 55
17. Rose L, Smith O, Gelinas C, Haslam L, Dale C, Luk E, et al. Critical care nurses' pain assessment and management practices: a survey in Canada. Am J Crit Care. 2012;21(4):251–9.
18. Watt-Watson J, Stevens B, Garfinkel P, Streiner D, Gallop R. Relationship between nurses' pain knowledge and pain management outcomes for their postoperative cardiac patients. J Adv Nurs. 2001;36(4):535–45.
19. Glynn G, Ahern M. Determinants of critical care nurses' pain management behaviour. Aust Crit Care. 2000;13(4):144–51.
20. Robinson BR, Mueller EW, Henson K, Branson RD, Barsoum S, Tsuei BJ. An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. J Trauma. 2008;65(3):517–26.
21. Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. Anesth Analg. 2010;111(2):451–63.
22. Awissi DK, Begin C, Moisan J, Lachaine J, Skrobik Y. I-SAVE study: impact of sedation, analgesia, and delirium protocols evaluated in the intensive care unit: an economic evaluation. Ann Pharmacother. 2012;46(1):21–8.
23. Kanji S, MacPhee H, Singh A, Johanson C, Fairbairn J, Lloyd T, et al. Validation of the critical care pain observation tool in critically ill patients with delirium: a prospective cohort study. Crit Care Med. 2016;44(5):943–7.
24. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE evidence to decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. BMJ. 2016;353:i2089.
25. Kavanagh BP. The GRADE system for rating clinical guidelines. PLoS Med. 2009;6(9):e1000094.
26. Kumar A, Miladinovic B, Guyatt GH, Schunemann HJ, Djulbegovic B. GRADE guidelines system is reproducible when instructions are clearly operationalized even among the guidelines panel members with limited experience with GRADE. J Clin Epidemiol. 2016;75:115–8.

27. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology. 2007;106(4):687–95; quiz 891–2
28. Mehta S, Burry L, Fischer S, Martinez-Motta JC, Hallett D, Bowman D, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. Crit Care Med. 2006;34(2):374–80.
29. Richards-Belle A, Canter RR, Power GS, Robinson EJ, Reschreiter H, Wunsch H, et al. National survey and point prevalence study of sedation practice in UK critical care. Crit Care. 2016;20(1):355.
30. Chawla R, Myatra SN, Ramakrishnan N, Todi S, Kansal S, Dash SK. Current practices of mobilization, analgesia, relaxants and sedation in Indian ICUs: a survey conducted by the Indian Society of Critical Care Medicine. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care. Medicine. 2014;18(9):575–84.
31. Wang J, Peng ZY, Zhou WH, Hu B, Rao X, Li JG. A national multicenter survey on management of pain, agitation, and delirium in intensive care units in China. Chin Med J. 2017;130(10):1182–8.
32. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. Crit Care Clin. 2009;25(3):431–49, vii
33. Muellejans B, Lopez A, Cross MH, Bonome C, Morrison L, Kirkham AJ. Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43755713]. Crit Care. 2004;8(1):R1–r11.
34. Karabinis A, Mandragos K, Stergiopoulos S, Komnos A, Soukup J, Speelberg B, et al. Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308]. Crit Care. 2004;8(4):R268–80.
35. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10(4):537–51.
36. Allouche S, Noble F, Marie N. Opioid receptor desensitization: mechanisms and its link to tolerance. Front Pharmacol. 2014;5:280.
37. Gaveriaux-Ruff C, Kieffer BL. Delta opioid receptor analgesia: recent contributions from pharmacology and molecular approaches. Behav Pharmacol. 2011;22(5–6):405–14.
38. Stein C. Opioid receptors. Annu Rev Med. 2016;67:433–51.
39. Zhang X, Bao L, Li S. Opioid receptor trafficking and interaction in nociceptors. Br J Pharmacol. 2015;172(2):364–74.
40. Anand KJ, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics. 2010;125(5):e1208–25.
41. Wiesenfeld-Hallin Z. Sex differences in pain perception. Gend Med. 2005;2(3):137–45.
42. Mogil JS, Bailey AL. Sex and gender differences in pain and analgesia. Prog Brain Res. 2010;186:141–57.
43. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. Crit Care Med. 2013;41(4):999–1008.
44. Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. The delta-opioid receptor: isolation of a cDNA by expression cloning and pharmacological characterization. Proc Natl Acad Sci USA. 1992;89(24):12048–52.
45. Contet C, Kieffer BL, Befort K. Mu opioid receptor: a gateway to drug addiction. Curr Opin Neurobiol. 2004;14(3):370–8.
46. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol. 2017;31(4):487–98.
47. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? Anaesthesia. 2016;71(11):1347–62.
48. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
49. Oh E, Ahn HJ, Sim WS, Lee JY. Synergistic effect of intravenous ibuprofen and hydromorphone for postoperative pain: prospective randomized controlled trial. Pain Physician. 2016;19(6):341–8.
50. Chabot-Dore AJ, Schuster DJ, Stone LS, Wilcox GL. Analgesic synergy between opioid and alpha2-adrenoceptors. Br J Pharmacol. 2015;172(2):388–402.

51. Pacreu S, Fernandez Candil J, Molto L, Carazo J, Fernandez Galinski S. The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. Acta Anaesthesiol Scand. 2012;56(10):1250–6.
52. Raffa R. Pharmacological aspects of successful long-term analgesia. Clin Rheumatol. 2006;25(Suppl 1): S9–15.
53. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010;56(6):514–7, e202–5.
54. Hanks F, McKenzie C. Paracetamol in intensive care - intravenous, oral or not at all? Anaesthesia. 2016;71(10):1136–40.
55. Suzuki S, Eastwood GM, Bailey M, Gattas D, Kruger P, Saxena M, et al. Paracetamol therapy and outcome of critically ill patients: a multicenter retrospective observational study. Crit Care. 2015;19:162.
56. Perbet S, Verdonk F, Godet T, Jabaudon M, Chartier C, Cayot S, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. Anaesthesia Crit Care Pain Med. 2018;37(6):589–95.
57. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs(NSAIDs) in children. Paediatr Anaesth. 2013;23(6):475–95.
58. Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to morphine-DEXCOM study). Anesthesiology. 2009;111(5):1075–84.
59. Zhao LH, Shi ZH, Chen GQ, Yin NN, Chen H, Yuan Y, et al. Use of dexmedetomidine for prophylactic analgesia and sedation in patients with delayed extubation after craniotomy: a randomized controlled trial. J Neurosurg Anesthesiol. 2017;29(2):132–9.
60. Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med. 2009;35(2):282–90.
61. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, et al. Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: a randomized controlled trial. Anesthesiology. 2016;124(2):362–8.
62. Papathanassoglou ED, Mpouzika MD. Interpersonal touch: physiological effects in critical care. Biol Res Nurs. 2012;14(4):431–43.
63. Myhren H, Toien K, Ekeberg O, Karlsson S, Sandvik L, Stokland O. Patients' memory and psychological distress after ICU stay compared with expectations of the relatives. Intensive Care Med. 2009;35(12):2078–86.
64. Kapfhammer HP, Rothenhausler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. Am J Psychiatry. 2004;161(1):45–52.
65. Myhren H, Ekeberg O, Toien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care. 2010;14(1):R14.
66. Duceppe MA, Perreault MM, Frenette AJ, Burry LD, Rico P, Lavoie A, et al. Frequency, risk factors and symptomatology of iatrogenic withdrawal from opioids and benzodiazepines in critically ill neonates, children and adults: a systematic review of clinical studies. J Clin Pharm Ther. 2018;44(2):148–56.
67. Arroyo-Novoa CMF-RM, Puntillo K. Identifying opioid and benzodiazepine withdrawal in trauma intensive care unit (TICU) patients. Crit Care Med. 2018;46(Suppl 1):791.
68. Clark J, Endicott J, Menon P, McMillian W. 919: incidence of prescribing opioids at hospital discharge after admission to a medical ICU. Crit Care Med. 2018;46(1):443.

Behavioral Therapies

K. J. Burdick, M. C. Courtney, and J. J. Schlesinger

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_16

Learning Objectives

The focus of this chapter is to analyze the characteristics of both post-traumatic stress disorder (PTSD) and post-intensive care syndrome (PICS), discuss the current forms of treatment and therapy for PTSD, and suggest novel behavioral therapies for the treatment of PICS. Two novel therapies, musical therapy and collaborative songwriting, have had previous success in improving the mental and physical health of other vulnerable populations, such as prisoners. A critical aspect of these forms of therapy is understanding the creative processes and benefits of lyrical and non-lyrical composition. Finally, with any form of therapy, it is important to assess their effectiveness, as well as the recovery and functionality of those suffering from PTSD and PICS.

16.1 Introduction

How can prison activities dictate what is done with patients in the intensive care unit (ICU)? How can common practice therapies come together with novel techniques and help treat serious disorders? People who have experienced some form of trauma, people who are considered part of a vulnerable population, are at risk for developing PTSD. This is a condition characterized by a trauma- and stressor-related disorder and is commonly linked to anxiety and other mental health issues. Similarly, patients discharged from the ICU can experience a trauma- and stressor-related disorder known as PICS.

16.2 Soldiers and ICU Patients: How Do They Relate?

16.2.1 Vulnerable Populations: What and Where They Are

Trauma occurs throughout life, and for most people, it is a temporary challenge; however, in 3.6% of men and 9.7% of women who experience a traumatic event, symptoms of fear and anxiety persist beyond the trauma itself [1]. This is characteristic of post-traumatic stress disorder (PTSD). In 1980, after the overwhelming number of soldiers from the Vietnam War experienced flashbacks and terrible distress, PTSD was officially added to the *Diagnostic and Statistical Manual of Mental Disorders 3* (DSM-3). Recently, the investigation of PTSD has expanded its scope from just those serving in the military to include a number of other vulnerable populations – such as prisoners, victims of abuse, and those with chronic health conditions. A vulnerable population is determined to the degree to which a population or individual is unable to anticipate, cope with, resist, and recover from the impacts of disasters [2]. Included within the scope of vulnerable populations who experience post-trauma symptoms are patients admitted into ICUs.

Educational Feature (Fig. 16.1)

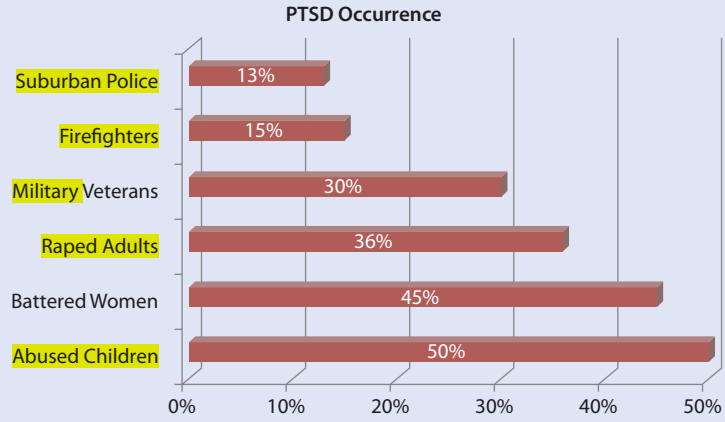


Fig. 16.1 Occurrence of PTSD in several vulnerable populations [3]

16.2.2 Post-traumatic Stress Disorder

The most recent DSM-5, published in 2013, defines PTSD as a disorder that develops in some people who have experienced a shocking, scary, or dangerous event who continue to experience problems such as stress or fear even when they are not in danger [4]. The flowchart shown in Fig. 16.2 demonstrates a potential model of PTSD. This figure shows the initial trauma being exacerbated by triggers and intrusive thoughts, further resulting in diagnosable PTSD. The symptoms of PTSD include physical, cognitive, and psychiatric factors. The psychiatric effects can range from an unprovoked fear response to anxiety and depression. In addition, the cognitive symptoms include decreased attention and memory recall. Finally, people may experience physical symptoms such as insomnia, nightmares, rapid weight loss, and increased startle response. According to the DSM-5, a diagnosis of PTSD requires satisfying criterion A–H, listed below.

A. The person was exposed to the following: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence.
B. The traumatic event is persistently re-experienced, in the following way(s):
   - Intrusive thoughts
   - Nightmares
   - Flashbacks
   - Emotional distress after traumatic reminders
   - Physical reactivity after traumatic reminders
C. Avoidance of trauma-related stimuli after the trauma, in the following way(s):
   - Trauma-related thoughts or feelings
   - Trauma-related reminders

D. Two required: Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):
   - Inability to recall key features of the trauma
   - Overly negative thoughts and assumptions about oneself or the world
   - Exaggerated blame of self or others for causing the trauma
   - Negative affect
   - Decreased interest in activities
   - Feeling isolated
   - Difficulty experiencing positive affect

E. Two required: Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):
   - Irritability or aggression
   - Risky or destructive behavior
   - Hypervigilance
   - Heightened startle reaction
   - Difficulty concentrating
   - Difficulty sleeping

F. Symptoms last for more than 1 month.

G. Symptoms create distress or functional impairment (e.g., social, occupational).

H. Symptoms are not due to medication, substance use, or other illness [4].

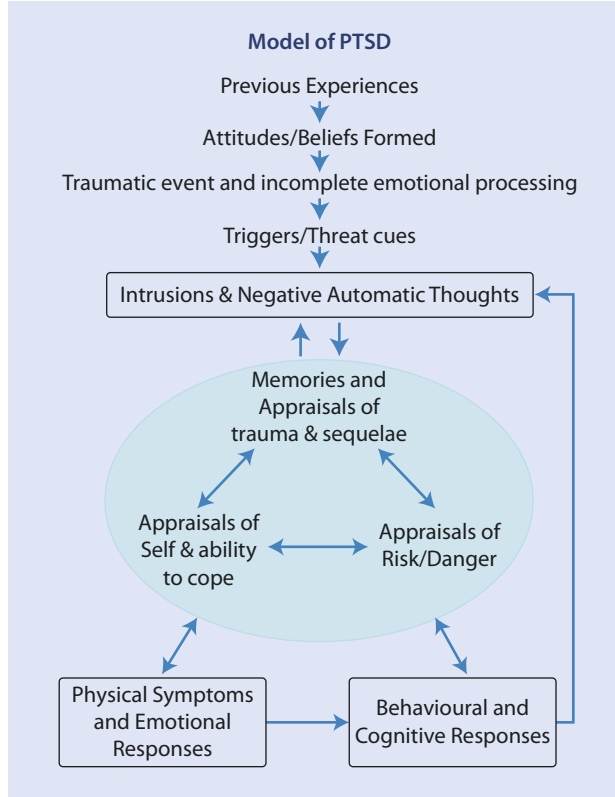


Fig. 16.2 Potential model of PTSD showing effects of predisposition, traumatic event, and resultant PTSD symptoms [5]

Diagnostic criteria are not met until at least 6 months after the trauma, although the onset of symptoms may occur immediately. Symptoms may last for 3 months to over a year [4]. With a combination of these psychiatric, cognitive, and physical PTSD symptoms, those affected experience a significant intrusion into their daily life.

16.2.3 ICU Patients: A Vulnerable Population

While the ICU is imperative to improving a patient's health, the ICU environment can simultaneously cause a threat to a patient's neuropsychological health, mimicking trauma experienced outside of the hospital. This environment of a patient's room is crowded and disruptive. Figure 16.3 shows the physical space of the ICU, depicting the general layout of closed rooms with the maximum number of beds that will fit. Care is provided to patients 24 hours a day, 7 days a week, by closely monitoring vital signs throughout the night with continuous monitor beeping and series of diagnostic tests. Figure 16.4 shows the proximity of these monitors to the patient, making the constant beeping even more so invasive.

This environment severely disrupts sleep and, furthermore, impacts cognitive performance, memory, concentration, and the patient's mood [6]. With impaired cognition, patients also commonly experience delusional memories regarding their ICU stay, which may further disturb their emotional stability and recovery [7]. In the ICU, 61% reported sleep deprivation, 94% said the analgesics requests did not relieve their pain, 62% had been afraid or anxious, and 46% had felt lonely or isolated [6].

This disruption, combined with the emotional stress and general concern for the patient's health that comes with being admitted to the ICU, can trigger high stress in both patients and family members. This prolonged stress can be equal to trauma in any other situation referenced before, such as being incarcerated or battling a chronic health condition. The treatment provided in an ICU is imperative; however, patients and family in this environment for an extended period of time are at risk for experiencing post-traumatic effects, just like prisoners and abuse victims develop PTSD.

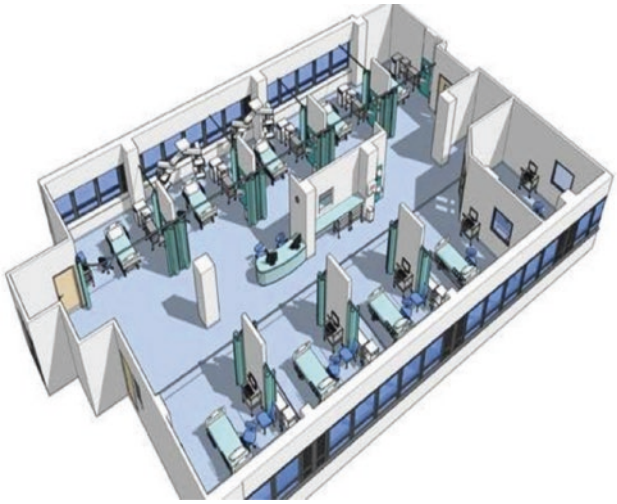


Fig. 16.3 ICU floor plan showing the central nursing station with surrounding patient rooms [8]

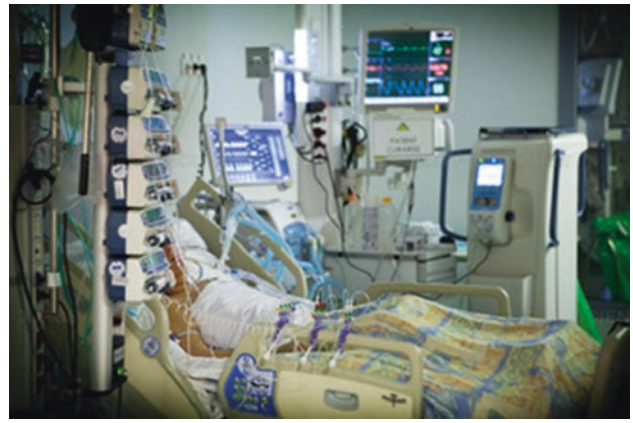


Fig. 16.4 Bed environment for a patient during their stay in the ICU. Pictured is the patient monitor in the top right. Below are the infusion pump and patient-controlled analgesia infusion device. To the left is the mechanical ventilator [9]

16.2.4 Post-intensive Care Syndrome (PICS)

Each year, 5 million patients in the United States and 300,000 patients in the United Kingdom are treated in an ICU. Of these patients, 50–70% will experience symptoms of post-intensive care syndrome (PICS) [10, 11]. Despite these high statistics, PICS is only now being recognized as a public health burden. PICS is defined as new or worsening impairment in physical, cognitive, or mental health status after critical illness and persisting beyond discharge from the ICU [12, 13]. PICS is a grouping of complications that include persistent cognitive dysfunction, debilitating weakness, and delusional and disturbing memories – similar to PTSD [14]. In addition to the disability of the patient, the families are also at risk to experiencing similar symptoms and developing post intensive care syndrome-family (PICS-F) [15, 16]. Many families may experience these symptoms when they feel they were left uninformed throughout the ICU stay or are grieving the loss of a loved one [13]. However, since the focus is on the patient, these family members are left unscreened and their symptoms unaddressed. To prevent this, it has been suggested that healthcare workers should focus on having inclusive conversations with families and allowing members to be part of the decision-making process.

As shown in Fig. 16.5, also similar to PTSD, the symptoms of PICS include physical, cognitive, and psychiatric effects. Physical symptoms may present as ICU-acquired neuromuscular weakness and pulmonary or neuromuscular impairment. Cognitive symptoms include declines in executive function, memory, and attention. Patients who experience delirium in the ICU, a severe state of confusion, are at a higher risk of developing worse cognitive symptoms of PICS [17]. Finally, the psychiatric symptoms include anxiety, depression, and, in the case of PICS-F, the burden of survivorship. Overall, PICS symptoms decrease patients' health-related quality of life (HRQoL) [6, 18, 19]. Figure 16.6 shows the various other factors that feed into the trauma and psychological disturbance experienced while in the ICU. These include, but are not limited to, prolonged sedation, hypoxemia, and sleep disturbances. Sleep disturbances are described as the occurrence of nightmares or insomnia, which prevent recovery and are detrimental to cognition and emotional regulation. Lack of sleep hinders physical recovery as it reduces the body's ability to function

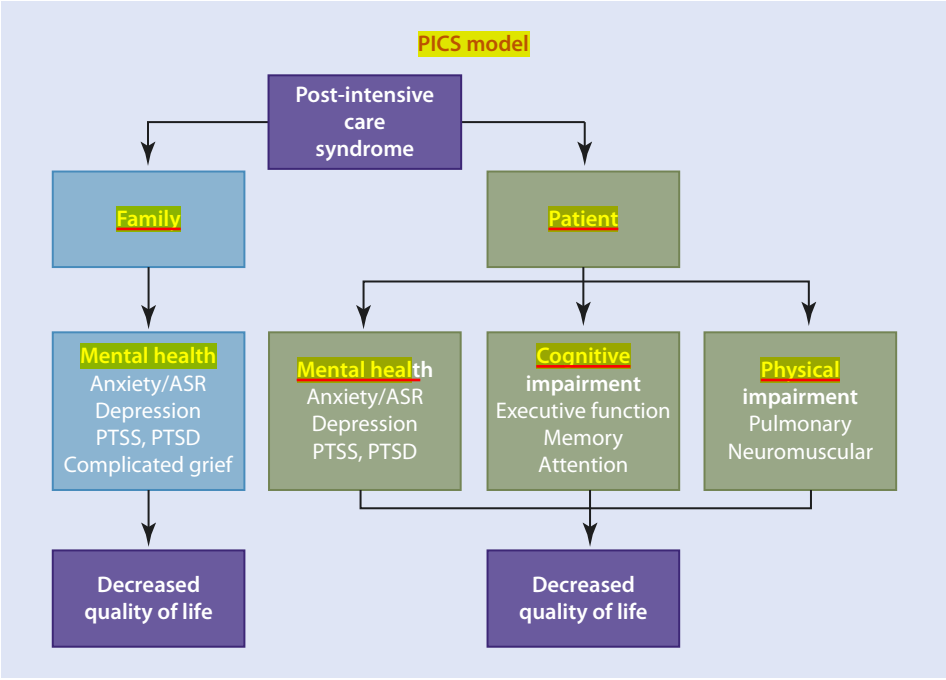


Fig. 16.5 Model of symptoms observed with PICS, showing the effects in both family and patients [22]

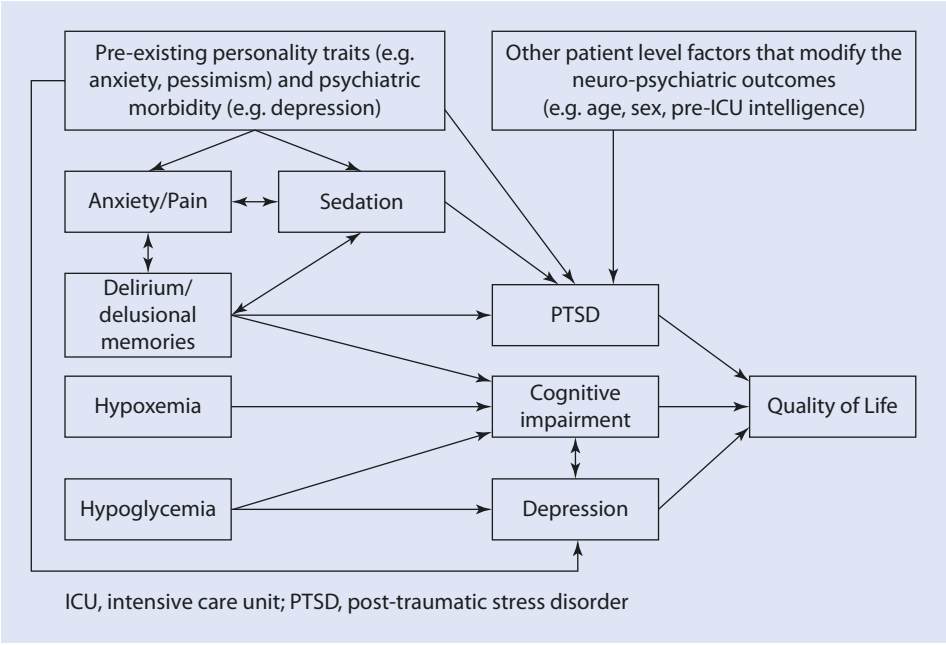


Fig. 16.6 Additional factors that contribute to the trauma and psychological disturbance experienced in the ICU [22]

properly and can, therefore, extend the illness of a patient in the ICU [20]. Current research indicates prolonged sedation, ventilation, and immobilization as leading risk factors for ICU patients developing PICS [21].

Similar to PTSD, symptoms may last months or years past discharge, depending on the patient. The main characteristic of PICS is that these symptoms arise or are worsened after recovering from a critical illness. These symptoms interfere with the patients' quality of life and, therefore, should be addressed and/or prevented.

Educational Feature: ICU Delirium Testimonial – I Was So, SO Consumed by Anxiety

"I don't remember most of the 40+ days I spent fighting ARDS in the ICU. I do remember bits, like snapshots – my Dad's warm wave and greeting when he arrived; I remember my Mom and sister lovingly giving me a bed-bath; I remember Dr. Wheeler and others talking. I also remember being asked questions over and over and answering by squeezing the questioner's hand. And I remember having my chest tube removed.

Unfortunately, I also remember being so overwhelmed by anxiety that my feet were in almost constant motion, back and forth, back and forth. My family began to recognize that when I shook my hands like that with my fingers splayed it meant that I wanted medication to help me tolerate the anxiety. They couldn't always give me anything.

Part of the time, I thought I was being restrained by elastic bands that held me down so that I couldn't move. The walls around me looked like I was being held in a multi-level pagoda. In my mind, I was plotting my escape to home, thinking I could pick at the threads of the imagined sewn elastic restraints and set myself free. Randomly I saw small Asian people who wouldn't look at me and I saw a black cat and a black pot-bellied pig. All the while, I was so, SO consumed by anxiety. Just remembering brings back shadows of anxiety." – Anonymous [23]

16.2.5 PTSD and PICS: Possible Treatment Overlap

As discussed in the previous two sections, there exist many similarities between PTSD and PICS. Both conditions are under the category of trauma- and stressor-related disorders and are characterized by lasting and inhibiting physical, cognitive, and psychological symptoms caused by some form of trauma. PTSD can be triggered by any traumatic event and may only affect the person who is directly involved. On the other hand, PICS is exclusive to post-ICU stays and may also present in other members in relation to the admitted patient.

The invasive nature of these symptoms in behavioral and cognitive function highlights the importance of timely diagnosis and rigorous treatment of these post-trauma symptoms in order to achieve effective therapy. With these correlations, therapies currently used for people struggling with PTSD should have a positive effect on both treating and preventing PICS.

Take-Home Messages

- Vulnerable populations include prisoners, abuse victims, chronically ill patients, and ICU patients.
- PTSD and PICS are two similar trauma- and stressor-related disorders triggered by some form of trauma or stressful incident and present with psychiatric, cognitive, and physical symptoms.
- PICS is caused exclusively after an ICU stay and is largely influenced by the length of sedation, ventilation, and immobilization. PICS can also affect more than just the patient experiencing the stressful stay in the ICU, for example, their family.

16.3 Multiple Modalities of Treatment and Therapy for PTSD

16.3.1 Established Therapy for PTSD

Many modalities of therapy have been established and researched that reduce the symptoms of PTSD. Such therapies include interpersonal, behavioral, technological, pharmacological, and musical, all of which may be incorporated into a treatment plan individually or in combination [24]. A patient may, therefore, be prescribed medications to reduce depression and anxiety, or pharmacological therapy, which is supplemented with social or cognitive behavioral therapy to encourage healthy thoughts and behaviors. While the many therapeutic options for PTSD and related disorders vary by efficacy, some are limited by the lack of study into their effects. Some treatments have been researched in trials that focus on the individual, some in group settings, and some have been researched in a very limited capacity. The effectiveness of the selected therapy, or combined therapy efforts, depends in part on the individual and their specific circumstances and symptoms. Variables such as age, gender, and proximity to trauma must be considered in the diagnosis and treatment of such disorders. Therefore, there is not one exclusive method for treating all patients with PTSD, but rather a range of established treatment options that may be recommended depending on physician discretion. Research trials continue to collect data that inform medical providers on the benefits and drawbacks of each mode of treatment, as well as investigate novel treatment options for PTSD [25].

16.3.2 Therapeutic Modalities

16.3.2.1 Behavioral Therapy

Behavioral therapy, specifically individual cognitive behavioral therapy (CBT), is a commonly prescribed treatment option for patients with PTSD. This approach addresses a patient's cognition or thought patterns, as well as behavior, or patterns of action. Mental healthcare professionals work with patients to understand their impaired thoughts, often attached to traumatizing memories and stimuli, and adjust their thinking to encourage healthy thoughts and emotional expression. This therapy aims to teach coping skills so that patients can manage and reduce symptoms on their own. In modifying the thoughts, emotions, and behaviors of an individual, this method minimizes the tendency of distorted cognitions to manifest as damaging behaviors. The category of behavioral therapy also encompasses eye movement desensitization and reprocessing (EMDR). This form of psychotherapy incorporates exposure to triggering stimuli and uses eye movements to allow a patient to experience their symptoms of fear and anxiety, understand the roots of such emotions, and begin to store memories of their experiences with a new and more positive perspective. Practices such as mindfulness, yoga, and acupuncture are also considered behavioral therapies that can aid in the management of PTSD symptoms and are especially popular in Eastern cultures [26]. CBT is typically administered over a period of months or years and, while an extensive time commitment, can offer a gradual path to healing via consistent support and guidance.

When assessing treatment options for PTSD, cognitive behavioral therapy is generally considered efficacious. Especially in initiating cognitive recovery, CBT has proven to be a crucial step in adjusting distorted cognitions and redirecting behaviors. While CBT is beneficial to many, Bryant et al. published findings that suggest some limitations to this

therapy. In patients that exhibit extreme amygdala activity, CBT is far less effective in providing coping skills. In patients who were less receptive to this treatment, the amygdala, or the component of the brain responsible for regulating fear, experienced an abnormal surge of activity in response to the presentation of feared stimuli [27]. This is assessed via fMRI, or functional magnetic resonance imaging. Therefore, individual differences must be considered when devising an individualized treatment plan to treat PTSD. The implications on PICS are comparable to those of PTSD, as patients in the ICU are exposed to trauma and experience similar symptoms that impair cognition and behaviors.

16.3.2.2 Technological Therapy

Technological therapy can be used to describe treatment that is implemented through technology. Internet-based therapy provides a treatment option for patients who are geographically isolated or hindered from obtaining in-person treatment due to fear of stigmatization. However, technological therapy often requires access to computers and various electronics, which creates a barrier to those with financial limitations. Patients with such limitations are able to receive coaching and gain access to mental healthcare professionals. New technologies also allow for the exploration of virtual reality. This mode of therapy immerses the patient in a sensory experience that mimics their trauma, which can be recreated in a visual, auditory, or haptic manner. Repeated exposure to a given feared stimulus can allow for an individual to manage their emotions surrounding the traumatic experience. Facing such anxiety in a safe environment supports a decrease in stress and increase in emotion management [26].

16.3.2.3 Pharmacological Therapy

Pharmacological therapy is commonly used in symptom management for PTSD and psychological disorders. The primary focus of pharmacological therapy is on antidepressant medication, with an emphasis on selective serotonin reuptake inhibitors (SSRIs) [25]. While cognitive behavioral therapies have a greater long-term efficacy, medications can be crucial in creating stability and reducing anxiety while a permanent treatment plan is established. Other varieties of medication have also been considered as an option in the prevention and treatment of PTSD. Propranolol, a beta-adrenergic blocker, acts as a protective measure against the onset of PTSD. As it blocks the reception of the neurotransmitter epinephrine, it allows memories to be stored with less emotional stress. This dissociation between memory and emotion may help reduce symptoms in PTSD patients. Prazosin, an alpha-1 adrenergic blocker, works to block excess norepinephrine, a neurotransmitter commonly released at night and correlated with nightmares. This medication may be beneficial in treating patients experiencing frequent flashbacks and nightmares [26]. Because PTSD symptoms stem from a fear response, medication can be ineffective in the presence of traumatic stimuli. Although pharmaceuticals do not address the psychological origins of PTSD, they assist in symptom management for many patients [26].

16.3.2.4 Group Therapy

Group therapy is often used in the treatment of PTSD and other psychological disorders to emphasize the importance of social relationships in recovery and promote interpersonal connection. Additionally, it identifies the direct impacts of trauma on such relationships and aids in mending or strengthening them. The family members of patients with PTSD often experience deep grief that can evolve into depression or anxiety. This mode of relational therapy can help both patients and their family members cope with the traumatic experiences that led to PTSD, as well as manage the symptoms of PTSD in a way

that fosters healthy relationships. Similarly, families of ICU patients experience distress and can benefit from participating in group therapy. Group cognitive behavioral therapy (GCBT), while not as well researched as individual cognitive behavioral therapy (CBT), is also used in treatment plans for PTSD patients. This approach teaches skills that allow patients to regulate their symptoms of stress and anxiety. The group context in which these skills are introduced allows for a collaborative learning environment and provides a more cost-efficient alternative to individual CBT. While the focus of group therapy supports a patient's social relationships, GCBT offers cognitive skills and training in a way that can also facilitate personal connection with others.

16.3.2.5 Therapeutic Music

Collaborative songwriting as therapy has proven to be effective in several vulnerable patient populations, such as prisoners, soldiers, and those with Parkinson's disease or traumatic brain injury. The resulting benefits in these populations can translate to individuals afflicted with PTSD or PICS. The application of this therapeutic model involves mentally and emotionally engaging the patient in the process of writing lyrics and music. The cognitive stimulation of the writing paired with the release that accompanies emotional reflection offers a dynamic combination. In addition to providing an outlet for expression and a coping mechanism to confront trauma, therapeutic music triggers multiple sensory pathways and results in an improvement of motor function [28]. While collaborative songwriting is not yet broadly practiced, it offers the potential to simultaneously improve cognitive, emotional, and motor functions in vulnerable populations. This therapeutic option will be explored in further detail in the remainder of the chapter.

16.3.3 Translation of PTSD Therapy to PICS: Symptomatic Overlap

While many treatment options exist for patients with PTSD, meta-analyses indicate a lack of partiality in the literature toward a singular treatment option [26]. As each of the therapeutic options previously discussed has proven efficacious in managing some aspect of PTSD for a given patient population, they have potential in managing and treating comparable afflictions such as PICS. The presentation of PICS, and its similarity to that of PTSD as shown in Fig. 16.5, allows for significant overlap in treatment options. As patients of both conditions commonly exhibit mental health deterioration in the form of anxiety and depression, the prescription of antidepressant drugs can help day-to-day management of depressive symptoms. In both patient populations, behavioral and interpersonal therapies have the potential to increase the quality of life and aid in the reintegration into society after a traumatic experience. Patients can also present with cognitive and physical deficiencies that result from trauma. In both PTSD and PICS patients, lapses in executive function and memory can be improved through cognitive behavioral and technological therapies. Finally, motor delays and other physical impairments can be addressed via pharmacological treatments and/or collaborative songwriting. Collaborative songwriting has also proven beneficial in treating cognitive symptoms of PTSD through emotional reflection and has significant potential in treating PICS. Because PTSD and PICS pose a multifactorial problem, as cognitive, emotional, behavioral, and physical consequences must be considered, it often requires a treatment approach that integrates the strengths of several healthcare professionals. Involving an interdisciplinary group of people, in and out of the hospital, proves important in both addressing symptoms and devising treatment from all angles.

Take-Home Messages

- PTSD patients may be prescribed some combination of interpersonal, behavioral, technological, pharmacological, and musical therapy to manage and treat their symptoms.
- CBT can be effective in preventing PTSD and PICS as well as improving individual functionality that has been impaired by such disorders.
- Therapeutic music offers an innovative approach to treat the psychological, emotional, social, and physical effects of PTSD and merits further study.

16.4 Previous Collaborative Songwriting and Musical Therapy Studies

Previous research with novel behavioral therapies, specifically musically related, have proven to be effective in treating both mental and physical post-trauma symptoms in other vulnerable populations, such as prisoners and ICU patients [29–31]. The musical and songwriting process is used to reflect on the traumatic experience and the surrounding emotions associated. This serves as an outlet for emotion and tool for reflection. With this evidence, musical therapy treatments could also be beneficial for ICU patients experiencing post-trauma symptoms or, furthermore, work to prevent these symptoms.

16.4.1 Songwriting with Prisoners

Time spent in jail can be stressful and traumatic. Educational programs have been shown to support prisoners enter back into society [32, 33]. Group musical therapy with prisoners was found to be effective in improving anxiety, depression, and self-esteem [34, 35]. Other groups specifically researched songwriting with prisoners. Their sessions consisted of group songwriting where the patients could socialize, express their feelings, and give each other advice and encouragement throughout the songwriting process. Songwriting therapy was found to improve pro-social skills, self-expression, relaxation, coping mechanisms, and anger management [29, 30]. The lyrics of songs written by the inmates in another songwriting program were analyzed using a coding strategy looking for development of certain positive themes. Their study concluded that the social and collaborative nature of songwriting with incarcerated men was beneficial in educational, psychological, social, and emotional avenues [36]. This previous implementation of collaborative songwriting and other forms of musical therapy prove to be effective in improving anxiety and overall self-esteem for the vulnerable population of incarcerated men.

16.4.2 Musical Therapy for Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder that primarily causes a number of movement complications, including tremors, bradykinesia, and rigidity. There are several pharmacological treatments for PD that can also be complemented by behavioral therapies, such as musical therapy. To implement music into therapy for physical

conditions, there must exist a link between the motor and auditory systems that has a true effect on physical conditions as it does with psychological. This link between the motor and auditory system is demonstrated at every concert, music lesson, and even car ride. When we hear music, it is a natural response to tap a finger or foot in rhythm with the beat. Rhythm is the local organization of musical time. It is the pattern of temporal intervals within a musical measure or phrase that in turn creates the perception of stronger and weaker beats [37].

To confirm this auditory-motor connection, researchers conducted two functional magnetic resonance imaging studies (fMRIs) to confirm that an auditory-perceptual event dissociated from an action process can still engage the motor system. In other words, it is known that thinking about a movement activates motor regions, but without the cognitive thought of a movement, is there still activation in the motor regions? The study was split into two groups. The first group participants were told to listen to the music in anticipation of tapping and, then later, to tap their finger along with the rhythm. The second group participants began by naively listening to the music without any instruction or action of finger tapping and then later were told to tap along with the rhythm. The findings indicated that the same motor regions of the brain were activated for study 1 with anticipation and study 2 naive listening, showing similar brain activation for motor and perceptual events initiated by the auditory system. This indicates that there exist an action-perception process and an inherent link between auditory and motor systems [35].

Through this research, the auditory-motor connection that would prove to be crucial to therapy in patients with PD is confirmed. With this auditory-motor connection in mind, musical therapy was used to improve both the motor and emotional symptoms of patients with PD. The musical therapy sessions included choral singing, rhythmic and free body movements, and active music involving collective invention. The effectiveness of the therapy was assessed by comparing pre-and post-test scores of the Unified Parkinson's Disease Rating Scale, Parkinson's Disease Quality of Life Questionnaire, and Happiness Measure. Overall, this study found musical therapy to be effective for motor, emotional, and behavioral functions in patients with PD. [28] The results of this study emphasize the impact that musical therapy has not only on emotional symptoms but also the physical symptoms of patients with PD and other vulnerable populations.

16.4.3 ICU Diaries: Proactive Self-Reflection

Knowing that PICS may develop during a patient's ICU stay, is there something a patient could do while in the ICU to prevent PICS symptoms from developing? In other terms – proactive therapy rather than reactive. A number of ICUs have conducted studies of diaries kept by healthcare providers recording the treatment for the duration of a patient's stay to assess its effectiveness on patient recovery. The requirements for the diary included secure diary storage, Polaroid camera, and diary guidelines at every bed space. The diary was kept by relatives, nurses, and others in simple language. A photograph was taken of the patient at the start and points of change. The diary contained daily information about their physical condition, procedures and treatments, events occurring on the unit, and significant events from outside the unit [38].

After their discharge from the hospital, patients were given the diaries to review. In 2010, study assessed patients using the ICU Memory Tool (ICUMT) on any delusional memories that had formed, and patients were given the diary that had been kept for them

during their ICU stay [31]. The study found that a diary explaining what happened to the patient in ICU was able to help patients fill in gaps in their memories, place any delusional memories into context, and aid psychological recovery. The study also notes that the diaries were beneficial to family members in their memory of the ICU stay to communicate better with the patient about their treatment. Other ICU diary studies also found a reduction in incidence of depression and anxiety for the patients and families based on the Hospital Anxiety and Depression Scale [38–40].

This study indicates that the practice of self-reflection and memory rehearsal are effective in not only treating but preventing post-trauma symptoms in ICU patients. The approach is similar to one of the goals of cognitive behavioral therapy, that the therapy serves to change how a patient thinks about their traumatic experiences. With this knowledge and detailed record of one's ICU stay, collaborative songwriting therapy can be more effective in reflecting and understanding the traumatic stress the patient experienced during their stay. The practice of diary keeping along with memory rehearsal is similar to the self-reflection implemented into collaborative songwriting therapy. *In this sense, collaborative songwriting is the musical exposition of the ICU diary.*

Educational Feature: Case Study, M.

M., an 18-year-old Caucasian female, began individual musical therapy sessions at the age of 16. M. was placed in foster care at the age of 13 after growing up with an abusive and alcoholic father. She continued to be abused in foster case and was once again removed from her living situation and placed into another foster home, where she resided at the time of this study.

M.'s communication skills were limited at the beginning. She often spoke softly and rapidly and was very self-critical. M. attended musical therapy in a private practice setting 1 session per week for a l-hour period for a total number of 75 sessions spanning a 26-month period.

To write the lyrics, M. and the therapist used brainstorming to make lists of and identify keywords and phrases to describe specific topics. After completing four songs and using musical therapy sessions to process her conflicting feelings, M. began to find things about herself that she liked. Creating songs provided M. with a much-needed means for expressing some of her painful and hidden emotions. As she was able to express some of these feelings, she began to discover her own strength and value. As a result, M. became more assertive with her ideas, and she experienced a newly found confidence in her ability to make decisions.

This study of the musical therapy experience of one adolescent suggests that songwriting can be an effective therapeutic tool when working with the sexual abuse survivor. M.'s progress in musical therapy demonstrates ways in which songwriting can help build self-esteem and provide survivors with a much-needed outlet for self-expression [41].

Take-Home Messages

- Songwriting with prisoners is effective for improving emotional issues.
- Musical therapy is effective on motor, emotional, and behavioral functions in patients with Parkinson's disease.
- ICU diaries were effective in aiding psychological recovery to prevent the onset of PTSD symptoms in ICU patients. They can also be used as reference points for songwriting therapy.

16.5 The Creative Process in Therapeutic Music: Benefits of Lyrical and Non-lyrical Composition

16.5.1 The Importance of the Creative Process

The ultimate goals of therapeutic music parallel the objectives of all modalities of psychological therapy. In short, it aims to improve mental health by introducing coping mechanisms that can be used to manage stress, anxiety, and depressive symptoms. Based on the existing literature on therapeutic music, this method of treatment improves the psychological well-being of the recipients as well as increases emotional regulation, motor functionality, and social reintegration. Additionally, it is shown to minimize psychological disorders, suicides, and overall economic burden in post-ICU patients [42]. The efficacy of this treatment in a wide range of applications prompts further investigation into the importance of the creative process of songwriting in an individual's healing.

The creative process of collaborative songwriting requires patients to deeply engage with their emotions, as well as describe what they are feeling through language. Even in non-lyrical musical therapy, the creative process involved in making music offers an emotional release, an outlet to express oneself in an artistic and meaningful way, as well as the ability to create a positive acoustic space. In this way, songwriting prompts coping and healthy emotion management, especially while revisiting emotions that characterize trauma. The exercise of songwriting, with or without lyrics, also requires a trained music therapist, as it involves the composition of music and creates an acoustic environment. As such, it requires interpersonal interaction and therefore fosters greater social functioning. Patients not only practice confronting their psychological burdens, but they do so in the presence of others, learning to expose their fears in a healthy and constructive way.

PICS patients, like PTSD sufferers, struggle to manage the fear response to stimuli that remind them of a traumatic experience. While the triggering stimuli may differ, both populations must learn to reintegrate into society despite psychological disturbances that cause anxiety, stress, and lack of emotion management. The creative process of songwriting redirects the emotion attached to trauma from internal stress toward a production of lyrics and instrumentals to encourage coping. In addition, the successful creation of a song as a product of therapy can lead to improvements in self-esteem and overall happiness [41]. Insight into the application and results of collaborative songwriting can be offered by the educational feature of "patient M." above. The benefits of such therapy extend beyond the intended psychological improvements to increase social and emotional functioning, enhancing the quality of life for post-ICU patients.

Finally, the benefits from the non-lyrical aspect of musical therapy include improvements in motor function as well as increases in relaxation and overall mental health. The link between auditory engagement and movement, investigated via auditory-motor neurons, incorporates an element of physical well-being to musical therapy, which is especially crucial for ICU patients with motor impairments [35]. The mental outlet for enjoyment and rest that music provides allows patients to temporarily escape their undesirable surroundings to focus on mental healing, rather than purely physical [29]. While the process of music creation has proven beneficial as a therapeutic method, the aspect of lyrical composition and expression of emotion through language may offer additional advantages.

16.5.2 Comparing Lyrical Versus Non-lyrical Therapeutic Music

Within the umbrella of musical therapy and collaborative songwriting exist several treatment approaches, including lyrical and non-lyrical composition techniques. Non-lyrical musical therapy can include active participation in music composition as well as active listening, in which one allocates their attentional resources to music as therapy. Non-lyrical musical therapy also plays a more general role when it establishes the tone of the acoustic environment in the ICU. Exposure to music in a setting such as the ICU is therapeutic in its promotion of relaxation and mental escape, which may alleviate stress and anxiety and, in turn, promote improvement in the mental stability and well-being of patients with PICS symptoms. As it induces relaxation, it may consequently improve physiological outcomes as well. An increase in relaxation may help stabilize the heart rate and breathing of critically ill patients, allowing the origin of an illness to be addressed and treated [43]. It also improves quality and quantity of sleep, allowing the body extended time to heal. Because it is the auditory-motor pathway that allows musical therapy to improve motor function, non-lyrical music may be sufficient to stimulate a motor response and encourage physical rehabilitation [28].

Finally, a study in 2009 provides evidence that musical therapy is beneficial to patients that have sustained traumatic brain injuries by improving aspects of executive functioning [44]. Thaut, prolific in the field of musical therapy, also stresses that one's behavior is influenced both by music and how it is both perceived and experienced. This finding supports musical therapy, not only as a means of achieving social and emotional improvement for patients but also as a central mode of neurobiological treatment and recovery for PICS [44]. Music perception stimulates cognitive processes and thus promotes improvement in executive function and mental flexibility. This increases a patient's ability to manage and shift attention between different tasks. Cognitive stimulation also improves emotional adjustment with regard to overcoming depression and anxiety [44]. A second finding reports that patients who suffer from disorders of consciousness demonstrate more progressed cognitive functioning when they are exposed to music they prefer, as opposed to an alternative sound experience [45]. Such studies recognize the potential of music to advance the cognitive recovery of patients. While non-lyrical musical therapy provides a myriad of neurocognitive benefits, the positive consequences of collaborative songwriting may be more extensive for some patients due to the added emotional and psychological benefits.

In addition to all the benefits previously discussed, collaborative songwriting provides an outlet for individuals to express their emotions. Because it often involves a patient's composition of words, it demands a deep level of emotional engagement. While addressing thoughts and emotions that are associated with trauma can be emotionally taxing at times, it provides an opportunity for greater psychological healing. It also allows for the healthy expression of grief and anger and contributes to a more positive overall effect. If collaborative songwriting is established as a long-term course of treatment, it can reveal the psychological progress of the patient. As original thoughts are the product of each therapy session, each song, or the evolution of sequential songs, can be assessed and used to gauge mental status and stability [41].

While lyrical musical therapy has added benefits, it is not always the most practical treatment option. As it combines the composition of both music and lyrics, it is typically accomplished with a professional songwriter, which can be a limiting factor in terms of time and availability. Considerations must also be made regarding cost, patient age and

background, as well as patient literacy; however, even for patients who lack proficiency in writing, practicing attaching words to emotions provides an added educational benefit [36]. Collaborative songwriting, although typically implemented with lyrics, can be done with or without a lyrical aspect involved. Whether lyrical or non-lyrical, musical therapy offers an innovative treatment option with minimal risk and maximal reward. Its potential to improve patient outcomes within the ICU as well as prevent and manage symptoms of PICS warrants further exploration and research.

16.5.3 The Acoustic Space of the ICU

As hospitals are designed to be sterile and efficient, they lack a sense of comfort that promotes healing and relaxation. Especially for critically ill patients that are cared for in the ICU environment for extended periods of time, the physical space could possibly contribute to symptoms of anxiety and depression. One way to transform the ICU into a more positive and healing atmosphere involves changing the acoustic space. Due to the monotonous beeping of patient monitors and medical devices, the ICU creates a stressful environment for the critically ill and their families. The incessant noise disrupts sleep and recovery, yet slight changes in the chirping of a monitor may generate fear. Because patient monitors have a low positive predictive value, an increase in volume of an alarm is rarely an indication of a real threat to patient safety; however, patients and families may feel neglected when caregivers respond to their alarms with a lack of urgency or timeliness. Although a delayed response time is typically a reflection of the caregiver's awareness of their patient's true urgency of care, it may be perceived as a lackadaisical approach [46].

The noise pollution of beeping monitors can also be detrimental to a clinician's ability to detect and effectually respond to shifts in patient alarms. Excessive environmental noise, such as slamming doors, people talking, and unattended monitors, can also hinder the accuracy and response time of a physician or nurse when responding to an urgent patient need [47]. To address this, the literature has suggested redesigning patient monitors with the expertise of an interdisciplinary group including, but not limited to, music therapists. Well informed on the cognitive aspects of pitch and tone, these professionals may offer ideas and insight into redesigned patient monitors that accurately reflect urgency and fluctuations with more pleasant sound [48].

16.5.3.1 The Sound Experience

After a prolonged hospital stay during which she was overwhelmed by the dissonance of typical hospital noise, sound alchemist, Yoko Sen, began her work, entitled "Transforming the Sound Experience in Hospitals." [49] As a patient, Sen experienced sound in a way that she believed negatively interfered with her recovery. In her attempts to improve the sound experience, Sen created meaningful ways to integrate music into hospitals for both patients and clinicians. Her novel research includes investigating the potential effects of designated tranquility rooms for healthcare providers. Even brief immersion in a tranquil environment that includes soothing music, dimmed lights, and pleasant scent may promote their own restoration and focus [49]. This may subsequently improve patient interactions and outcomes. Finally, she proposes that patients prefer "human-centered" sound, including music and sounds of nature, rather than the "disease-centered" sounds of monitors and machines. An adjustment to the overall sound of the ICU could prove very beneficial in improving the health and happiness of the critically ill.

The introduction of musical therapy, tranquility rooms, and adapted patient alarms that better convey physiological information at a noise level that reflects the urgency of patient need would not only produce therapeutic results, but it would also shift the dynamic of the ICU to a more pleasant one. As Yoko Sen acknowledges, a human's auditory abilities are the last of the five senses to cease upon death. As sound is the final earthly connection that patients experience when dying, a more positive acoustic space is necessary.

16.5.4 Implementation and Cost Considerations

The implementation of a musical therapy program into an ICU or an entire hospital requires significant cost considerations. Whether lyrical or non-lyrical music composition, a board-certified music therapist is necessary to conduct treatment. Like many psychological therapies, this cost could fall under the responsibility of the individual patient; however, those with low socioeconomic status or no insurance are at a disadvantage and are economically unable to comply with their prescribed treatment plan. If the hospital were to absorb the salary of a full-time music therapist, it may have to adjust costs elsewhere, but it would be more widely beneficial. One possible method of integration could involve the presence of a music therapist during rounds with the ICU team. This approach would allow the therapist to become familiar with each individual patient so that they can best generate a musical therapy plan that targets specific patient needs. Increased access to musical therapy also allows for further research into its value as a method of treatment. Furthermore, the long-term economic impact of more PICS patients in the workforce because of musical therapy may merit government funding to assist in implementation of the program. While there is no current model of implementation or application of musical therapy on a large-scale, the effects of the treatment suggest that its benefits would extend beyond the patient.

Take-Home Messages

- The process of music creation offers therapeutic benefits to PTSD and PICS patients.
- Collaborative songwriting can include lyrical and non-lyrical, both of which provide patients with cognitive stimulation and allow them to express their emotions in a creative way.
- The acoustic space of the ICU can be detrimental to both patients and physicians but may be improved through implementing therapeutic music, introducing tranquility rooms, as well as adjusting patient monitors.
- The application of musical therapy in hospitals may differ based on cost considerations.

16.6 Assessing Effectiveness of Novel Therapies

There needs to be a method for assessing the benefit of these novel approaches to treatment. When examining the symptoms of post-traumatic disorders, they all interfere the daily life of those who are experiencing these symptoms. One possible option is an assessment of a patient's ability to complete their activities of daily living (ADLs) and instrumental activities of daily living (IADLs).

ADLs can be represented by the acronym "DEATH": Dress, Eat, Ambulate, Toilet, Hygiene. "If you can't do your ADL's, you're dead" [50]. While a bit morbid, these post-trauma symptoms may present serious life impairments and challenges. ADLs are assessed using the Katz Index of Independence in Activities of Daily Living. Clients are scored yes/no depending on independence of six daily activities. A 1 is given if the client can complete the activity independently, and a 0 is given if they cannot. Impairment is assessed on a 0–6 scale, with 2 or below indicating severe impairment and 6 indicating full function [51].

IADLs are more advanced skills and assess ability for independent living, such as using transportation, taking medicine, and managing money. The IADLs are assessed using the Lawton-Brody Instrumental Activities of Daily Living Scale. Similar to the Katz Index, patients are scored 0–1 in eight different categories of daily activities that are more advanced than those assessed on the Katz Index. Impairment is assessed on a 0–8 scale, with 0 indicating low function, high dependence, and 8 indicating high function, low dependence [52]. Both the ADLs and IADLs are critical for self-care and must be addressed in a patient to determine their level of individual function.

Take-Home Messages

- ADLs and IADLs are critical assessments to determine level of individual function and, therefore, benefit of therapy treatment.
- PTSD and PICS both severely impair day-to-day functionality, and individual considerations must be made when devising treatment plans.

16.7 Recovery and Functionality

The symptoms of PTSD and PICS are debilitating and often impede daily living. In populations with high rates of PTSD in children, such as war-torn nations, the use of narrative exposure therapy shows potential to improve neurocognitive recovery [53]. Furthermore, preventing PTSD from manifesting in children who have been exposed to trauma is a challenge. Some studies argue that early interventions focused on cognitive behavioral therapy minimize the risk of developing chronic PTSD [54].

Like many psychological disorders, both PTSD and PICS have the potential to severely impair an individual's physical and emotional functionality. This includes the ability to operate normally in social relationships, manage emotions, cognitively process information, and maintain physical health. The functional recovery process for patients with PTSD and PICS can be extensive and require several methods of therapy used in conjunction. Just as war veterans and trauma victims are challenged with the repercussions and ongoing symptoms of PTSD, PICS patients must prepare to integrate into normal life after their release from the hospital.

In a study by Maier, the pattern of functional recovery was evaluated in healthy patients after the administration of general anesthesia. By measuring brain function with electroencephalography, researchers could monitor the order in which cognitive functions, such as memory, attention, and logic, return. Neurocognitive testing can be administered by computer and can include assessments such as the "Motor Praxis Task," which is a time-sensitive test of the sensorimotor cortex and requires patients to track and click certain areas of the screen. The "Psychomotor Vigilance Test" records reaction times to a presented stimulus and

does not produce scores that improve with practice, while the "Digital Symbol Substitution Test" analyzes the functionality of the temporal and prefrontal cortices through the decoding of symbols. Furthermore, the "Fractal-2-Back" challenges a patient's ability to engage their working memory, the "Visual Object Learning Test" measures the memory of three-dimensional structures, and the "Abstract Matching Test" tests the ability of a patient to exercise executive function in abstract object classification [55]. This evaluation goes beyond the typical assessment of cognitive functioning that is based on simple commands to gauge a person's neurocognitive capabilities and better understand their recovery progress. While a lack of clear understanding still exists regarding the timeline of patient's cognitive functionality when emerging from anesthesia, a similar protocol could be developed to assess the regaining of cognitive abilities in PICS patients. Establishing a standard pattern of neurocognitive recovery could aid caretakers in devising practical treatment plans as well as provide patients with awareness and expectations of their recovery.

Take-Home Messages

- Searching for a pattern in cognitive recovery and functionality could be beneficial for patients and physicians.

Conclusion

Trauma- and stressor-related disorders such as PTSD and PICS are invasion to multiple avenues of a person's life. There are various forms of treatment used to treat PTSD, including behavioral and pharmacological; however, the novel musical approach to both stress disorders proves effective and promising.

In vulnerable populations, such as prisoners, people with chronic disease, and ICU patients, the central theme of self-reflection and changing the way a person views their traumatic experience are crucial to the effectiveness of their therapy and, eventually, recovery. In cases like the ICU diaries, patients were able to create a concrete account of their experience and, when coupled with collaborative songwriting, can turn their experience into something beautiful and reflective. The creative process involved in music composition, both lyrical and non-lyrical, is the key to accessing its therapeutic benefits. Musical therapy, collaborative songwriting, in particular, allows ICU patients a healthy outlet to express emotion and offers both cognitive stimulation and social interaction. It is also shown to improve motor function and diminish PICS symptoms such as depression and anxiety but teaching coping skills.

Musical therapy also has the potential to induce a positive shift in the acoustic space of the ICU. Noise pollution from patient alarms and the overall hectic atmosphere of a hospital can be detrimental to recovery. As musical therapy has the power to establish a more positive acoustic environment, it can improve the health and sound experience of the critically ill. While the implementation of this therapy is dependent on different cost considerations, integrating a music therapist into patient rounds could generate an individualized and maximally beneficial therapy plan.

Finally, it is important to establish methods of measurement for patient progress as well as maintain perspective regarding the path to recovery. Scales such as the Katz and Lawton-Brody help provide insight on the effectiveness of an individual's treatment. Future research is necessary to establish a standard for recovery and a timeline of functionality but would be highly beneficial in creating awareness among PICS patients and caretakers.

PICS poses a threat to the emotional, mental, physical, and social well-being of the critically ill. Standard treatments show success in some patients, but not all. To address all patients and continue to advance in medical care, novel therapies need to be utilized. Collaborative songwriting demonstrates success in improving a patient's symptoms, quality of life, and overall treatment. Where traditional treatments fall short, collaborative songwriting and other novel behavioral therapies are there to continue on the road to full recovery.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62(6):593–602.
2. Vulnerable Groups: World Health Organization; 2002 [cited 2018 February 1]. Available from: http://www.who.int/environmental_health_emergencies/vulnerable_groups/en/.
3. Shalev AY, Freedman S, Peri T, Brandes D, Sahar T, Orr SP, Pitman RK. Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry. 1998;155(5):630–7.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
5. Cambridge CaE. What is post traumatic stress disorder (PTSD)? CBT and EMDR Cambridge. Available from: www.cbtandemdr-cambridge.co.uk/what-is-post-traumatic-stress-disorder-ptsd.
6. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. J Transl Intern Med. 2017;5(2):90–2.
7. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001;29(3):573–80.
8. Sahi P, Patel S. ICU Floor Plan. In: Plan IF, editor. Jhansi, India: Organization of Intensive Care Unit; 2014. p. ICU floor plan showing the central nursing station with surrounding patient rooms.
9. Benoist A. Intensive care patient. Retrieved from: https://www.sciencesource.com/archive/Intensive-Care-Patient-SS2679829.html.
10. Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010;38(1):65–71.
11. Winter J. Hospital adult critical care activity. Redditch: National Health Service; 2017.
12. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9. (1530-0293 (Electronic)).
13. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome–family. Crit Care Med. 2012;40(2):618–24.
14. Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, et al. Exploring the scope of post–intensive care syndrome therapy and care: engagement of non–critical care providers and survivors in a second stakeholders meeting. Crit Care Med. 2014;42(12):2518–26.
15. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, Annane D, et al. Risk of posttraumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171(9):987–94. (1073-449X (Print)).
16. Anderson WG, Arnold RM, Angus DC, Bryce CL. Posttraumatic stress and complicated grief in family members of patients in the intensive care unit. J Gen Intern Med. 2008;23(11):1871–6.
17. Davidson JE, Hopkins RO, Louis D, Iwashyna TJ. Medicine SoCC.: Society of Critical Care Medicine; 2013. Available from: http://www.myicucare.org/Thrive/Pages/Post-intensive-Care-Syndrome.aspx.
18. Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry. 2008;30(5):421–34.
19. Maley JH, Brewster I, Mayoral I, Siruckova R, Adams S, McGraw KA, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. Ann Am Thorac Soc. 2016;13(8):1351–60.
20. Gilbert KS, Kark SM, Gehrman P, Bogdanova Y. Sleep disturbances, TBI and PTSD: implications for treatment and recovery. Clin Psychol Rev. 2015;40:195–212.

21. Torres J, Veiga C, Pinto F, Ferreira A, Sousa F, Jacinto R, et al. Post intensive care syndrome – from risk at ICU admission to 3 months follow-up clinic. Intensive Care Med Exp. 2015;3(1):A448.
22. Randall Lane R. Post-ICU syndrome. After the ICU2016. Retrieved from: http://maryland.ccproject.com/2016/06/15/lane-fall-after-the-icu-post-intensive-care-syndrome/.
23. Anonymous. Patient Testimonials Patient Testimonials|ICU Delirium and Cognitive Impairment Study Group: VUMC Center for Health Services Research; 2013 [cited 2018 January 31]. Available from: http://icudelirium.org/testimonials.html.
24. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. PLoS One. 2012;7(6):e38915.
25. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. J Clin Psychiatry. 2013;74(6):e541–50. (1555–2101 (Electronic)).
26. Cukor J, Spitalnick J, Difede J, Rizzo A, Rothbaum BO. Emerging treatments for PTSD. Clin Psychol Rev. 2009;29(8):715–26.
27. Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, et al. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med. 2008;38(4):555–61.
28. Pacchetti C, Mancini F, Aglieri R, Fundaro C, Martignoni E, Nappi G. Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation. Psychosom Med. 2000;62(3):386–93. (0033–3174 (Print)).
29. Gallagher LM, Steele AL. Music therapy with offenders in a substance abuse/mental illness treatment program. Music Ther Perspect. 2002;20(2):117–22.
30. Rio RE, Tenney KS. Music therapy for juvenile offenders in residential treatment. Music Ther Perspect. 2002;20(2):89–97.
31. Jones C, Bäckman C, Capuzzo M, Egerod I, Flaatten H, Granja C, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. Crit Care. 2010;14(5):R168.
32. Harer MD. Prison education program participation and recidivism: a test of the normalization hypothesis. Washington, DC: Federal Bureau of Prisons; 1995.
33. Mendonça M. Gamelan in prisons in England and Scotland: narratives of transformation and the "good vibrations" of educational rhetoric. Ethnomusicology. 2010;54(3):369–94.
34. Christian G, Jörg A, Kjetil H, Liv Gunnhild Q, Fiona Kirkwood B, Anita Lill H, et al. Music therapy for prisoners: pilot randomised controlled trial and implications for evaluating psychosocial interventions. Int J Offender Ther Comp Criminol. 2013;58(12):1520–39.
35. Chen JL, Penhune VB, Zatorre RJ. Listening to musical rhythms recruits motor regions of the brain. Cereb Cortex. 2008;18(12):2844–54. (1460–2199 (Electronic)).
36. Mary LC, Catherine MW. Inside the fences: pedagogical practices and purposes of songwriting in an adult male U.S. state prison. Int J Music Educ. 2017;35(4):541–53.
37. Zatorre RJ, Chen JL, Penhune VB. When the brain plays music: auditory–motor interactions in music perception and production. Nat Rev Neurosci. 2007;8:547.
38. Knowles RE, Tarrier N. Evaluation of the effect of prospective patient diaries on emotional well-being in intensive care unit survivors: a randomized controlled trial*. Crit Care Med. 2009;37(1):184–91.
39. Bergbom I, Svensson C, Berggren E, Kamsula M. Patients' and relatives' opinions and feelings about diaries kept by nurses in an intensive care unit: pilot study. Intensive Crit Care Nurs. 1999;15(4):185–91.
40. Garrouste-Orgeas M, Coquet I, Périer A, Timsit J-F, Pochard F, Lancrin F, et al. Impact of an intensive care unit diary on psychological distress in patients and relatives. Crit Care Med. 2012;40(7):2033–40.
41. Lindberg KA. Songs of healing: songwriting with an abused adolescent1. Music Ther. 1995;13(1):93–108.
42. Noyes EM, Schlesinger JJ. ICU-related PTSD – a review of PTSD and the potential effects of collaborative songwriting therapy. J Crit Care. 2017;42:78–84. (1557–8615 (Electronic)).
43. Mofredj A, Alaya S, Tassaioust K, Bahloul H, Mrabet A. Music therapy, a review of the potential therapeutic benefits for the critically ill. J Crit Care. 2016;35:195–9.
44. Thaut MH, Gardiner JC, Holmberg D, Horwitz J, Kent L, Andrews G, Donelan B, et al. Neurologic music therapy improves executive function and emotional adjustment in traumatic brain injury rehabilitation. Ann N Y Acad Sci. 2009;1169:406–16. (1749–6632 (Electronic)).

45. Castro M, Tillmann B, Luaute J, Corneyllie A, Dailler F, Andre-Obadia N, et al. Boosting cognition with music in patients with disorders of consciousness. Neurorehabil Neural Repair. 2015;29(8):734–42. (1552–6844 (Electronic)).
46. Edworthy J. Alarms are still a problem! Anaesthesia. 2013;68(8):791–4.
47. Stevenson RA, Schlesinger JJ, Wallace MT. Effects of divided attention and operating room noise on perception of pulse oximeter pitch changes: a laboratory study. Anesthesiology. 2013;118(2):376–81.
48. Schlesinger JJ, Stevenson RA, Shotwell MS, Wallace MT. Improving pulse oximetry pitch perception with multisensory perceptual training. Anesth Analg. 2014;118(6):1249–53.
49. Sen YK. Transforming the sound experience in hospitals: STIR 2016; 2016. Retrieved from: https://vimeo.com/203202091.
50. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86.
51. Shelkey M. Katz index of independence in activities of daily living (ADL). Hartford Inst Geriatr Nurs. 2012;2:1–2.
52. Graf C. The Lawton instrumental activities of daily living scale. AJN Am J Nursing. 2008;108(4):52–62.
53. Neuner F, Onyut PL, Ertl V, Odenwald M, Schauer E, Elbert T. Treatment of posttraumatic stress disorder by trained lay counselors in an African refugee settlement: a randomized controlled trial. J Consult Clin Psychol. 2008;76(4):686–94.
54. Galatzer-Levy IR, Ankri Y, Freedman S, Israeli-Shalev Y, Roitman P, Gilad M, et al. Early PTSD symptom trajectories: persistence, recovery, and response to treatment: results from the Jerusalem Trauma Outreach and Prevention Study (J-TOPS). PLoS One. 2013;8(8):e70084.
55. Maier KL, McKinstry-Wu AR, Palanca BJA, Tarnal V, Blain-Moraes S, Basner M, et al. Protocol for the Reconstructing Consciousness and Cognition (ReCCognition) Study. Front Hum Neurosci. 2017;11:284.

Post-intensive Care Syndrome in Relatives of Critically Ill Patients

Audrey de Jong, Nancy Kentish, Virginie Souppart, Samir Jaber, and Elie Azoulay

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_17

Learning Objectives

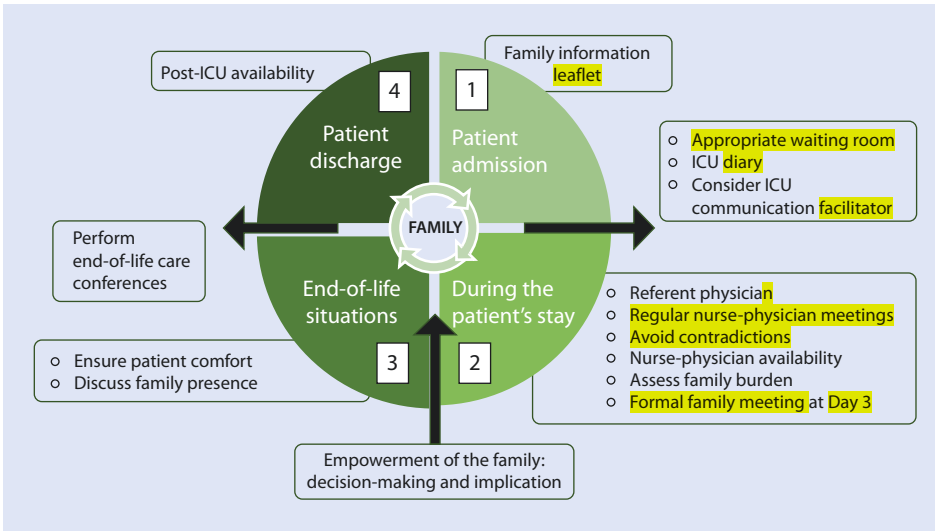
After reading this chapter, the learner will be able to understand:

- That anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms are frequent in relatives of ICU patients
- The importance to decrease family burden and how to implement several strategies to lessening them
- That up to 40% of family members suffer from at least one psychiatric illness 1 year after the patient's ICU stay
- How a family information leaflet, an appropriate waiting room, and the use of an ICU diary and of an ICU communication facilitator should be implemented by the ICU team

17.1 Introduction

In recent years, while technical improvements have been translated into increase of survival rates in critically ill patients, physicians and nurses in intensive care units (ICUs) have developed a strong interest in family members, creating the concept of family-centred care [1–4].

Awareness of the distress experienced by families of ICU patients is increasing, and family members are no longer considered as simple visitors to the ICU. On the contrary, family members receive dedicated communication aiming to reduce their psychological burden during and after the ICU stay. Studies have been conducted both to assess the health impact of the ICU experience on family members and to measure the effects of preventive interventions. Anxiety, depression, post-traumatic stress disorders (PTSD), and cognitive dysfunction are the main psychological impairments observed in family members. These conditions are known as post-intensive care syndrome – family, or PICS-F [5]. Strategies aiming to decrease family burden in ICUs [6] will be detailed in this chapter and are summarized in ◘ Figs. 17.1 and 17.2.



◘ **Fig. 17.1** Tools and strategies available to decrease family burden in intensive care units. ICU intensive care unit

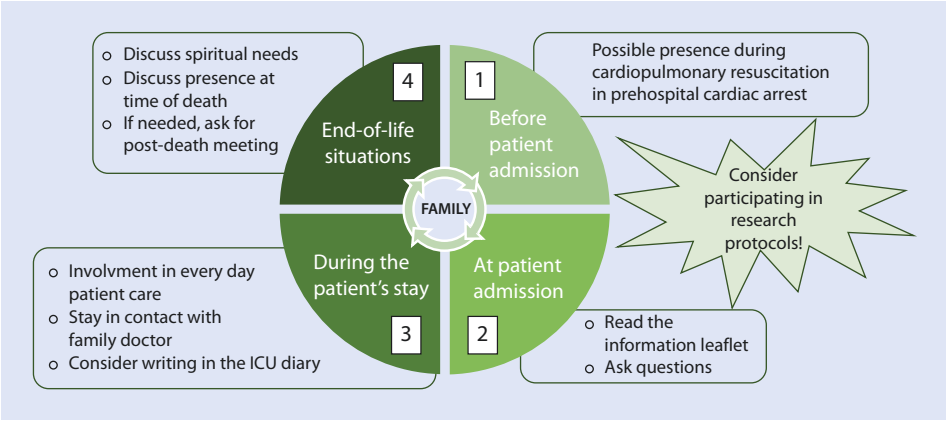


Fig. 17.2 Empowering family members to decrease their burden in intensive care units. ICU intensive care unit

17.2 Anxiety and Depression

Anxiety and depression are symptoms that can considerably alter a person's quality of life and can hinder their understanding of a situation. Symptoms of anxiety and depression can be detected using the Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaith in 1983 [7] which is a 14-item self-screening questionnaire. Seven items evaluate depression and seven items assess anxiety. Each item is scored on a 0–3 scale, so that scores can range from 0 to 21 for anxiety and 0 to 21 for depression. The HADS takes only 2–5 min to complete. These symptoms are common in relatives of ICU patients, as shown in many studies.

In a French prospective multicentre study [8], symptoms of anxiety or depression were present in 73% of family members and 84% of spouses. Risk factors for anxiety and depression symptoms were identified, including non-modifiable factors such as age and female gender. Modifiable factors were the absence of regular physician and nurse meetings, the absence of a room used only for meetings with family members, the absence of a waiting room, and perceived contradictions in the information provided by caregivers. When defining the organization and policies of their ICU, caregivers should bear in mind the need to decrease the risk of anxiety and depression in family members. Based on these data, these steps should include holding regular nurse-physician meetings to discuss patient and family needs, having a dedicated information room, having a waiting room, and ensuring that there are no contradictions in the information given to families. In a complementary study [9], it was found that in 54% of cases, the representative failed to understand the diagnosis, prognosis, or treatment of the patient. Physician-related factors of poor comprehension were a first meeting with representative <10 min and failure to give the relative an information brochure.

In order to improve family members' experience, a preventive strategy, aimed to increase family understanding and satisfaction and decrease symptoms of anxiety and depression, was assessed, using a family information leaflet (FIL), in addition to standard information [10]. The leaflet aims to give simple, practical information to people whose relatives are admitted to the ICU. It includes general information about the ICU and hospital, with phone numbers, visiting hours, a diagram of a typical ICU room, and a glossary.

A prospective randomized controlled trial [10] was performed in 34 French ICUs, assessing comprehension of diagnosis, prognosis, treatment, satisfaction with information, and anxiety and depression according to the providing or not of the FIL. Interestingly, anxiety and depression rates were not significantly different between the two randomized groups, whereas comprehension and satisfaction in the representatives with good comprehension were significantly improved in the FIL group.

In spite of an increase in ICU survival rates, end-of-life in these units remains frequent. The implications are major not only for patients but also for relatives, with important consequences for our health-care system. Family burden (i.e. the negative impact of ICU experience) increases when the patient dies in the ICU [11]. Different strategies have been tested, both during the patient's hospitalization and after the patient's death, to improve family experience in the months that follow the patient's death.

Among these strategies, end-of-life family conferences have been developed. These are formal, structured meetings between intensivists (physicians, nurses, etc.) and family members. During these conferences, family members and ICU caregivers discuss the patient's situation in a quiet room. Ideally, family members are given opportunities to ask questions, express concerns, and confront painful emotions with the help of empathetic professionals. End-of-life conferences were specifically assessed in family members of 126 patients dying in 22 ICUs in France in a randomized controlled study [12], showing that these meetings are associated with a significant decrease in anxiety and depression symptoms 3 months after the patient's death. These results further highlight that quality of communication is at the heart of family members' experience.

Strategies to improve family experience are most often developed during the patient's ICU stay. However, a recent multicentre randomized controlled trial [13], the first strategy testing outside the ICU, was designed to test the hypothesis that a condolence letter, compared to no condolence letter, could reduce grief symptoms in families of patients who had died in the ICU. Among the 242 patients, 123 were included in the intervention letter group and 119 in the control group. After 6 months, the results were unexpected: the HADS score was significantly worse in the intervention group than in the control group. The prevalence of depression symptoms and the HADS-depression subscale score were also higher in the intervention group. The use of a systematic condolence letter does not seem useful to reduce symptoms of anxiety and depression in families.

Different end-of-life situations coexist in ICUs, including brain death followed by organ donation request. Family members are at the centre of the decision process as within a limited time frame the team will first announce brain dead and approach relatives about organ donation. Experience of the organ donation process and grief symptoms in relatives of brain dead patients who discussed organ donation in the ICU was recently assessed in a multicentre longitudinal study in 28 ICUs in France [14]. Relatives of non-donor patients reported less support both from the ICU team and during discussions with the coordination team. They were less satisfied with communication with the ICU team and reported less communication about organ donation with the ICU clinicians than relatives of donor patients. More than half of the relatives of non-donors described the decision as difficult and were dissatisfied with the process. Interestingly, the decision to consent to or to refuse organ donation was not associated with anxiety or depression over the 3 months that followed the patient's death. However, this study highlights the importance of quality communication whatever the family's decision.

The main studies assessing anxiety and depression of families are shown in Table 17.1. Clinicians should be aware that anxiety and depression symptoms are frequent in relatives

Table 17.1 Main studies assessing anxiety and depression

Study	Type of study	Number of family members	Main results
Pochard et al. *CCM* 2001 [8]	Prospective multicenter study in 43 ICUs	920	Symptoms of anxiety or depression were present in 72.7% of family members.
			Three groups of factors associated with symptoms of anxiety were identified: patient-related (absence of chronic disease), family-related (spouse, female gender, desire for professional psychological help, help being received by general practitioner), and caregiver-related (absence of regular physician and nurse meetings, absence of a room used only for meetings with family members).
			Three groups of factors associated with symptoms of depression were identified: patient-related (age), family-related (spouse, female gender, not of French descent), and caregiver-related (no waiting room, perceived contradictions in the information provided by caregivers).
Azoulay et al. *AJRCCM* 2002 [10]	Prospective randomized trial in 34 French ICUs	175	If comprehension and satisfaction were improved in family information leaflet group compared to control group, anxiety and depression assessed using HADS score did not differ between groups.
Azoulay et al. *CCM* 2004 [15]	Prospective multicenter study in 78 ICUs in France	357	The HADS score indicated anxiety in 399 (73%) family members and depression in 192 (35%).
Lautrette et al. *NEJM* 2007 [12]	Prospective multicenter study in 22 ICUs	126	The median HADS score was lower in the intervention group (end of life family conference), and symptoms of both anxiety and depression were less prevalent.
Garrouste et al. *CCM* 2012 [16]	Prospective single-center study	143	An ICU diary significantly decreased anxiety at 3 months, but not depression.
Jabre et al. *NEJM* 2013 [17]	Randomized multicenter study in 15 prehospital emergency medical service units	570	In the intervention group, 211 of 266 relatives (79%) witnessed CPR, as compared with 131 of 304 relatives (43%) in the control group. Relatives who did not witness CPR had symptoms of anxiety and depression more frequently than those who did witness CPR.
Curtis et al. *AJRCCM* 2016 [18]	Randomized bicenter trial in two hospitals	268	An ICU communication facilitator was associated with decreased depressive symptoms at 6 months.

(continued)

Table 17.1 (continued)

Study	Type of study	Number of family members	Main results
Kentish-Barnes et al. *ICM 2017* [13]	Multicenter randomized trial in 22 ICUs in France	242	In relatives of patients who died in the ICU, a condolence letter failed to alleviate grief symptoms and may have worsened depression symptoms.
Kentish-Barnes et al. *AJRCCM* 2018 [14]	Multicenter longitudinal study in 28 ICUs in France	202	Experience of organ donation processes varies between relatives of donor versus non-donor patients, the latter experiencing more difficulty and burden. However, the decision to donate (consent/refusal) is not associated with grief symptoms.

ICU intensive care unit, *HADS* hospital anxiety and depression scale

of ICU patients, especially during and after end-of-life situations. A family information leaflet at the ICU patient admission [10], an appropriate waiting room, regular nurse-physicians meetings to discuss patient and family needs and to avoid contradictions [8], and end-of-life family conferences [12] could help reduce anxiety and depression symptoms of ICU patients' relatives (Fig. 17.1). Interestingly, a recent qualitative study showed that participation in bereavement research is often beneficial for family families and can be developed [19].

17.3 Post-traumatic Stress Disorder

PTSD is a psychological reaction resulting from a situation in which the physical and/or psychological integrity of the patient and/or his/her relatives has been threatened and/or actually affected (including serious accident, violent death, rape, aggression, illness serious, war, and attack). The coping skills of the subject are overwhelmed. The immediate reaction may have been intense fear, helplessness, or horror. In DSM-5, PTSD belongs to the trauma and stress-related disorder category. Individuals who suffer from PTSD systematically avoid any event or discussion leading to his emotions. Despite these strategies, the event keeps coming back to the person's mind in flashback or nightmare. PTSD can lead to clinical impairment in important areas of functioning.

PTSD is not rare for families of ICU patients. In a longitudinal European study of Azoulay et al. [20], the stress-related morbidity among family members 90 days after ICU discharge or death was assessed and showed that post-traumatic stress reaction, defined as an impact of event scale (IES) score greater than 30, was found in one-third of family members 90 days after ICU discharge or death of a relative. Risk factors for post-traumatic stress reaction were information perceived as unsatisfactory and sharing end-of-life decisions, as confirmed in another study of the same FAMIREA group [15]. It was also suggested that empowerment of relatives, involving them in every day patient care, bathing, feeding, and aspiration [20], could help reduce the occurrence of PTSD.

PTSD of relatives of dying patients in ICU has been specifically evaluated. An American study [21] assessed PTSD in family members of patients who died in 11 Washington State hospitals. Families with psychological symptoms were more likely to report that access to a counsellor ($P < .001$) and information about spiritual services might have been helpful while the patient was in the ICU ($P = 0.024$). The identification and correction of these factors may help decrease the rate of PTSD symptoms in families of end-of-life patients. Another study of the same group [11] focused on PTSD symptoms among family members of patients who died in the ICU. Family members of older patients had lower scores for PTSD ($P = 0.026$). Family members that were present at the time of death ($P = 0.021$) and family members of patients with early family conferences ($P = 0.012$) reported higher symptoms of PTSD. When withdrawal of a ventilator was decided, family members reported lower symptoms of depression ($P = 0.033$). In order to assess, in a reproducible and standardized manner, the experience of relatives of patients who die in the ICU, the CAESAR study [22] aimed to develop a specifically designed instrument. The CAESAR score was computed and was strongly associated with post-ICU PTSD in the relatives. This score could be used to identify families at risk and as a primary endpoint in clinical studies. In particular, as also underlined in the study by Kross et al. [11], the finding that family members present at time of death have higher symptoms of PTSD suggests that it may be important to counsel family members accordingly and to allow each individual to make the choice that is best for him or her.

Other strategies have been developed to increase both the patient's and the relatives' well-being, such as an ICU diary [16]. The ICU diary is written for ICU patients during their time of sedation and ventilation. It is written by relatives, nurses, and others. Once conscious, the patient can read the diary in order to better understand what happened in the ICU. Although the ICU diary was initially developed for the patient, this study shows that it also affects family members' well-being and decreases symptoms of PTSD 12 months after the experience.

As found for anxiety and depression symptoms, end-of-life family conferences may also help to reduce PTSD symptoms [12]. In a study mentioned above [12], customized end-of-life family conferences, including provision of a brochure on bereavement, resulted in longer meetings in which families felt more supported in making difficult decisions, had more opportunities to speak and to express emotions, were more likely to accept realistic goals of care, and experienced more relief from guilt. These combined effects allowed the decrease incidence of PTSD.

In the particular setting of cardiopulmonary resuscitation (CPR) performed outside the hospital, with subsequent admission to the ICU, a multicentre randomized trial [17] showed that giving family members of patients undergoing CPR the option of witnessing the resuscitation sequence was associated with a significantly lower incidence of PTSD-related symptoms than the standard practice regarding family presence. It is worth noting that whether or not the family members were offered the choice, more favourable results of psychological testing were noted when family members were present. This study highlights that relatives can sometimes be considered as active partners rather than passive observers.

Communication with the family of critically ill patients is often insufficient [23], and poor communication is associated with family distress [12]. In light of these findings, an

American research team [18] has developed the concept of an ICU communication facilitator, i.e. a social worker or a nurse trained to improve communication between the family and the ICU team. Their interventional study aimed to improve discussions about goals of care and palliative care in the ICU by improving communication between the families and the ICU team. However, there were no significant differences in psychological symptoms at 3 months or anxiety or PTSD at 6 months. The intervention was associated with decreased depressive symptoms at 6 months.

The main studies assessing PTSD symptoms in family members are shown in Table 17.2. Relatives of patients hospitalized in ICU are at high risk of PTSD symptoms. PTSD occurrence significantly alters family, social, and professional life on a daily basis. To reduce this risk, it is important to improve the quality of communication with the patient and his family: using an ICU diary to make sense of the stay in intensive care, psychological support, and improvement of end-life-care and communication. Raising clinicians' awareness to this risk makes it possible to identify high-risk individuals and develop appropriate care for patients and/or their relatives during the ICU stay (Fig. 17.1) and in the months following the ICU stay.

Table 17.2 Main studies assessing post-traumatic stress disorder and cognitive dysfunction

Study	Type of study	Number of family members	Main results
Azoulay et al. *AJRCCM* 2005 [20]	Prospective multicenter study in 21 ICUs	284	Post-traumatic stress symptoms were found in 94 (33.1%) family members.
			Higher rates were noted among family members who felt information was incomplete in the ICU (48.4%), who shared in decision-making (47.8%), whose relative died in the ICU (50%), whose relative died after end-of-life decisions (60%), and who shared in end-of-life decisions (81.8%).
Lautrette et al. *NEJM* 2007 [12]	Prospective multicenter study in 22 ICUs	126	The participants in the intervention group (end-of-life family conference) had a significantly lower median IES score than the 52 participants in the control group (27 vs. 39, $P = 0.02$) and a lower prevalence of PTSD-related symptoms (45% vs. 69%, $P = 0.01$).
Siegel et al. *CCM* 2008 [24]	Prospective monocenter study	41	In a cohort of bereaved next of kin of patients who died in the ICU, 34% met criteria for at least one psychiatric illness: major depressive disorder (27%), generalized anxiety disorder (10%), panic disorder (10%), or complicated grief disorder (5%). Disorders were more common in spouses than other kinship relations, those experiencing additional stressors after the loss, those who said the patient was ill <5 years, and those who said the patient's physician was not comforting.

Table 17.2 (continued)

Study	Type of study	Number of family members	Main results
Gries et al. *Chest* 2010 [21]	Substudy of a randomized multicenter trial in 15 ICUs	226	Prevalence of PTSD and depressive symptoms were 14.0% and 18.4%, respectively. Family characteristics associated with increased symptoms included female gender (PTSD; depression), knowing the patient for a shorter duration (PTSD, depression), and discordance between family members' preferences for decision-making and their actual decision-making roles (PTSD; depression). Depressive symptoms were also associated with lower educational level.
Kross et al. *Chest* 2011 [11]	Substudy of a randomized multicenter trial in 15 ICUs	226	Family members of older patients had lower scores for PTSD. Family members that were present at the time of death and family members of patients with early family conferences reported higher symptoms of PTSD. When withdrawal of a ventilator was ordered, family members reported lower symptoms of depression.
Garrouste et al. *CCM* 2012 [16]	Prospective single-center study	143	An ICU diary significantly affected posttraumatic stress-related symptoms in relatives and surviving patients 12 months after ICU discharge.
Jabre et al. *NEJM* 2013 [17]	Randomized multicenter study in 15 prehospital emergency medical service units	570	In the intervention group, 211 of 266 relatives (79%) witnessed CPR, as compared with 131 of 304 relatives (43%) in the control group. The frequency of PTSD-related symptoms was significantly higher in the control group than in the intervention group and among family members who did not witness CPR than among those who did.
Curtis et al. *AJRCCM* 2016 [18]	Randomized bicenter trial in two hospitals	268	An ICU communication facilitator was not associated with significant differences in psychological symptoms at 3 months or anxiety or PTSD at 6 months.
Kentish-Barnes et al. *ICM* 2016 [22]	Prospective multicenter study in 41 ICUs in France	600	The CAESAR score 21 days after death in the ICU is strongly associated with post-ICU burden in the bereaved relatives. The CAESAR score should prove a useful primary endpoint in trials of interventions to improve relatives' well-being.
Kentish-Barnes et al. *ICM* 2017 [13]	Multicenter randomized trial in 22 ICUs in France	242	In relatives of patients who died in the ICU, a condolence letter failed to alleviate grief symptoms and may have worsened PTSD-related symptoms.

ICU intensive care unit, *CPR* cardiopulmonary resuscitation, *PTSD* post-traumatic stress disorder

17.4 Cognitive Dysfunction

Though data on long-term outcomes in families is limited, it appears that up to 40% of family members suffer from at least one psychiatric illness 1 year after the patient's ICU stay. Siegel and coworkers [24] performed a small study on the incidence of psychiatric illness in 41 relatives who were primary surrogate decision-makers before the death of a relative in a medical ICU. Among the 41 relatives, 34% presented criteria for at least one psychiatric illness: major depressive disorder (27%), generalized anxiety disorder (10%), panic disorder (10%), or complicated grief disorder (5%). These disorders were more frequent in spouses (63% vs. 16% of other relatives) and in relatives reporting that the physician had not been comforting (71% vs. 23%).

While family members are initially relieved that their loved one is "out of the woods" and leaving the ICU, a new world is just beginning, and adjustments can be difficult to navigate, let alone recognize. The person who was in the ICU is no longer "just" the spouse, parent, or child, he or she often becomes a person with multiple needs and, in some way, remains a patient. Three months after their ICU stay, 40% of patients have global cognition scores of 1.5 SD which is below the population means [25]. The relative thus becomes a caregiver and is trusted into a role that he or she is not necessarily equipped to deal with, especially without the support and all-encompassing care of the ICU staff. After discharge from the ICU, caregivers frequently realize just how exhausted they are: physically and emotionally, and perhaps there is a financial toll, as well. The focus is intently on the patient, as is necessary, while the needs of the caregiver are often ignored [26]. This can lead to a set of psychological symptoms that family members frequently experience but do not have a means to express, as anxiety, depression, PTSD, or cognitive dysfunction. Little is known about the real incidence of cognitive dysfunction in families of ICU patients, in particular in the long run after the patient's ICU discharge or death.

17.5 Time Points for Family Management

International guidelines for family-centred care in the ICU have recently been developed [6]. The time points which are crucial for family management are threefold [27]. First, in the 48 h following ICU admission, comprehension, satisfaction, and symptoms of anxiety and depression should be assessed to answer the family's specific needs, to improve the likelihood that timely and adequate information is provided, and to screen for symptoms of anxiety and/or depression which might affect participation in the decision-making process. Second, at day 3, a routine formal family meeting should be held, using a communication strategy that best fits the family's needs. Specific information requested by families must be provided, comprehension should be evaluated by reviewing the medical facts, a care plan should be scheduled, and the family's hopes should be discovered and discussed. Third, in case of shift from curative care to comfort care, a formal end-of life family conference helps reduce family burden and may decrease the risk of subsequent complicated grief. In light of recent interventional studies [13, 28, 29], new communication strategies for patients discharged alive from the ICU and for their relatives should be developed and evaluated.

Conclusion

Anxiety, depression, and PTSD symptoms are frequent in relatives of ICU patients. In order to decrease family burden, several strategies can be implemented by the ICU team (◘ Fig. 17.1), including empowerment of family members (◘ Fig. 17.2). A family information leaflet, an appropriate waiting room, and the use of an ICU diary and of an ICU communication facilitator should be implemented by the ICU team. The information given should be complete, avoiding contradictions. In end-of-life situations, the family may choose to share or not the decision and to be present or not, the comfort of patient continuously ensured, and the end-of-life conferences performed. Family members can also be proactive by asking questions, reading the information leaflet, writing in the ICU diary, being involved in every day patient care (feeding, bathing, aspiration), and staying in contact with the family doctor.

Take Home Messages

- The information given should be complete, avoiding contradictions
- Anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms are frequent in relatives of ICU patients
- In order to decrease these symptoms, some fundamental steps should be followed, including regular nurse-physician meetings to discuss patient and family needs, having a dedicated information room, having a waiting room, and ensuring that there are no contradictions in the information given to families
- End-of-life family conferences should be developed. These are formal, structured meetings between intensivists (physicians, nurses, etc.) and family members during which the patient's situation is discussed in a quiet room. Ideally, family members are given opportunities to ask questions, express concerns, and confront painful emotions with the help of empathetic professionals
- As found for anxiety and depression symptoms, end-of-life family conferences may also help to reduce PTSD symptoms
- New communication strategies for patients discharged alive from the ICU and for their relatives should be developed and evaluated
- Physicians, nurses, and family doctors have to stay in contact with family members

Funding and Conflict of Interest Support was provided solely from institutional and/or departmental sources.

All authors declare the absence of any involvement in any organization with a direct financial interest in the subject of the manuscript.

References

1. Azoulay E, Pochard F, Chevret S, Lemaire F, Mokhtari M, Le Gall JR, et al. Meeting the needs of intensive care unit patient families: a multicenter study. Am J Respir Crit Care Med. 2001;163(1):135–9.
2. Curtis JR, Patrick DL, Shannon SE, Treece PD, Engelberg RA, Rubenfeld GD. The family conference as a focus to improve communication about end-of-life care in the intensive care unit: opportunities for improvement. Crit Care Med. 2001;29(2 Suppl):N26–33.

3. Heyland DK, Rocker GM, Dodek PM, Kutsogiannis DJ, Konopad E, Cook DJ, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. Crit Care Med. 2002;30(7):1413–8.
4. Azoulay E, Sprung CL. Family-physician interactions in the intensive care unit. Crit Care Med. 2004;32(11):2323–8.
5. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. Crit Care Med. 2012;40(2):618–24.
6. Davidson JE, Aslakson RA, Long AC, Puntillo KA, Kross EK, Hart J, et al. Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. Crit Care Med. 2017;45(1):103–28.
7. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
8. Pochard F, Azoulay E, Chevret S, Lemaire F, Hubert P, Canoui P, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. Crit Care Med. 2001;29(10):1893–7.
9. Azoulay E, Chevret S, Leleu G, Pochard F, Barboteu M, Adrie C, et al. Half the families of intensive care unit patients experience inadequate communication with physicians. Crit Care Med. 2000;28(8):3044–9.
10. Azoulay E, Pochard F, Chevret S, Jourdain M, Bornstain C, Wernet A, et al. Impact of a family information leaflet on effectiveness of information provided to family members of intensive care unit patients: a multicenter, prospective, randomized, controlled trial. Am J Respir Crit Care Med. 2002;165(4):438–42.
11. Kross EK, Engelberg RA, Gries CJ, Nielsen EL, Zatzick D, Curtis JR. ICU care associated with symptoms of depression and posttraumatic stress disorder among family members of patients who die in the ICU. Chest. 2011;139(4):795–801.
12. Lautrette A, Darmon M, Megarbane B, Joly LM, Chevret S, Adrie C, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. 2007;356(5):469–78.
13. Kentish-Barnes N, Chevret S, Champigneulle B, Thirion M, Souppart V, Gilbert M, et al. Effect of a condolence letter on grief symptoms among relatives of patients who died in the ICU: a randomized clinical trial. Intensive Care Med. 2017;43(4):473–84.
14. Kentish-Barnes N, Chevret S, Cheisson G, Joseph L, Martin-Lefevre L, Si Larbi AG, et al. Grief symptoms in relatives who experienced organ donation request in the ICU. Am J Respir Crit Care Med. 2018;198(6):751–8.
15. Azoulay E, Pochard F, Chevret S, Adrie C, Annane D, Bleichner G, et al. Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. Crit Care Med. 2004;32(9):1832–8.
16. Garrouste-Orgeas M, Coquet I, Perier A, Timsit JF, Pochard F, Lancrin F, et al. Impact of an intensive care unit diary on psychological distress in patients and relatives*. Crit Care Med. 2012;40(7):2033–40.
17. Jabre P, Belpomme V, Azoulay E, Jacob L, Bertrand L, Lapostolle F, et al. Family presence during cardiopulmonary resuscitation. N Engl J Med. 2013;368(11):1008–18.
18. Curtis JR, Treece PD, Nielsen EL, Gold J, Ciechanowski PS, Shannon SE, et al. Randomized trial of communication facilitators to reduce family distress and intensity of end-of-life care. Am J Respir Crit Care Med. 2016;193(2):154–62.
19. Kentish-Barnes N, McAdam JL, Kouki S, Cohen-Solal Z, Chaize M, Galon M, et al. Research participation for bereaved family members: experience and insights from a qualitative study. Crit Care Med. 2015;43(9):1839–45.
20. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171(9):987–94.
21. Gries CJ, Engelberg RA, Kross EK, Zatzick D, Nielsen EL, Downey L, et al. Predictors of symptoms of posttraumatic stress and depression in family members after patient death in the ICU. Chest. 2010;137(2):280–7.
22. Kentish-Barnes N, Seegers V, Legriel S, Cariou A, Jaber S, Lefrant JY, et al. CAESAR: a new tool to assess relatives' experience of dying and death in the ICU. Intensive Care Med. 2016;42(6):995–1002.
23. Fassier T, Darmon M, Laplace C, Chevret S, Schlemmer B, Pochard F, et al. One-day quantitative cross-sectional study of family information time in 90 intensive care units in France. Crit Care Med. 2007;35(1):177–83.

24. Siegel MD, Hayes E, Vanderwerker LC, Loseth DB, Prigerson HG. Psychiatric illness in the next of kin of patients who die in the intensive care unit. Crit Care Med. 2008;36(6):1722–8.
25. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
26. Schmidt M, Azoulay E. Having a loved one in the ICU: the forgotten family. Curr Opin Crit Care. 2012;18(5):540–7.
27. Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. Crit Care Med. 2009;37(10 Suppl):S448–56.
28. Curtis JR, Back AL, Ford DW, Downey L, Shannon SE, Doorenbos AZ, et al. Effect of communication skills training for residents and nurse practitioners on quality of communication with patients with serious illness: a randomized trial. JAMA. 2013;310(21):2271–81.
29. Carson SS, Cox CE, Wallenstein S, Hanson LC, Danis M, Tulsky JA, et al. Effect of palliative care-led meetings for families of patients with chronic critical illness: a randomized clinical trial. JAMA. 2016;316(1):51–62.

Psychological Impairment in Professional Caregivers

Bara Ricou

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_18

ICU caregivers including physicians, nurses, and nurse assistants are at high risk of moral distress and burnout [1, 2]. The incidence of burnout among the caregivers varies according to medical specialties and differs slightly between the professions. It occurs in 20–50% of physicians in emergency, surgery, or internal medicine [3–5] and in 30–50% of ICU caregivers including physicians, nurses, and nurse assistants [1, 6, 7]. The readers might wonder why the editors inserted a chapter about ICU caregivers inside this book designed for patients and family members. The reason is that the mental well-being of ICU professional is of major importance for the care of the patients [8] and at the same degree of their relatives. Indeed, the caregivers in mental distress are unable to take care of the patients, are disengaged, and become insensitive to others' suffering [3].

The preceding chapters report how important is the sustained care for the critically ill patients, especially when the length of ICU stay is prolonged. In addition, the care for the chronic critically ill patients can be cumbersome, and their relatives are demanding [9]. These patients require not only the ICU acute care skills but also an additional humane approach that is time consuming and difficult to provide in this special environment. This requirement can be a source of stress for intensive caregivers [10].

Other psychological impairments were described among the ICU professional. Indeed, the prevalence of post-traumatic stress disorder (PTSD) is increased among the ICU nurses compared to general nurses [11]. The repeated confrontation with suffering patients and relatives may lead to compassion fatigue [12] that in turn can increase the feeling of dissatisfaction in the job.

Learning Objectives

The following paragraphs will present the factors associated with the psychological impairment in ICU caregivers and the essential arguments leading to the care of the caregivers. The diagnostic tools to approach the mental distress among healthcare professionals and the potential treatments will be addressed.

18.1 The Associated Factors

The factors associated with the occurrence of moral distress and burnout in ICU caregivers are numerous (Table 18.1). Some are general in many healthcare services, whereas some are specific to the ICU.

Two major factors lead the ICU caregivers to high risk of mental health disturbances.

- Their special personality: the profile of the personal who choose critical care is remarkable. He/she is conscientious, self-critical, very demanding with oneself, perfectionist, and (too) much involved in whatever the task and sensitive to others' feelings but not enough with themselves [18].
- The special working environment: the ICU is an incredibly psychologically and physically aggressive and burdensome work environment for the clinicians. The critical medicine is a very demanding specialty: it requires a high standard of knowledge and technicity and actions in tight timeliness, in parallel with human competence such as empathy. It needs high skills in communication for interpersonal

Table 18.1 Associated factors with the occurrence of burnout, moral distress, compassion fatigue, or PTSD among the ICU caregivers

Type of psychological impairment	Type of caregivers affected	Associated factors favoring the occurrence	References
Burnout	Physicians	Female gender	[13]
		Workload (nights, period of work)	
		Conflicts (with nurses, colleagues)	
	Nurses, nurse assistants	Older age	[6]
		Inability to choose days off	
		No participation in an ICU research group	
		Conflicts (with patients, head nurse, physicians)	
		Care for dying patient	
		Decisions to forgo life-sustaining therapy	
	Physicians, nurses, nurse assistants	Male gender	[1]
		Being a nurse assistant	
		Proportion of male nurse among the team	
		No child	
		Young age below 40	
		End-of-life care	
		Mortality	
	Nurses, nurse assistants	Lack of patients' cooperation	[14]
		Managing work constraints and private life	
		Always performing	
		Relationship (patients, families, colleagues)	
	Nurses	Staffing	[15]
Moral distress, depression	Physicians	Dissatisfaction with career	[16]
		Lack of recognition	
		Too much responsibility	
		Stress on personal/family life	
		Keeping up to date with knowledge	
		Making the right decision alone	

(continued)

Table 18.1 (continued)

Type of psychological impairment	Type of caregivers affected	Associated factors favoring the occurrence	References
	Physicians, nurses	Perceived inappropriateness of care	[2]
		Too much care	
		Symptoms control only by physicians	
		No involvement of nurses for EOL decision	
		Bad collaboration between nurses and physicians	
		Freedom to decide how to perform tasks	
		Poor teamwork	
	Physicians, nurses, and other (PICU)	Ethical dimensions of practice	[17]
		Fear, mistrust, hostility in the management–staff relationship	
		Hierarchy	
		Difficulties in team work	
		No liberty of expression	
		Lack of emotional support	
	Physicians	Repeated stressful experiences	[7]
		Organization:	
		Workload	
		Impaired relationships	
		Burnout	
Compassion fatigue or STS	Nurses	BO and CF predict STS	[12]
		Negative coworker relationship	
		Years in current position	
		Hours per shift	
		Time in direct patient care	
		Medication	

Table 18.1 (continued)

Type of psychological impairment	Type of caregivers affected	Associated factors favoring the occurrence	References
PTSD	Nurses	End-of-life care	[11]
		Postmortem care	
		Seeing patients die	
		Verbal abuse (family members, physicians, nurses)	
		Wounds, bleeding, injuries	
		Performing "futile" care	
		Performing CPR	
		Workload	

PTSD post-traumatic stress disorder, *EOL* end-of-life, *PICU* paediatric ICU, *STS* secondary traumatic stress, *BO* burnout, CF compassion fatigue, *CPR* cardio pulmonary resuscitation

collaboration and supporting patients and relatives in great distress in an atmosphere of stress and fear of death, where conflicts are frequent. End-of-life decision [19] and care [1, 6, 13], conflicts [20], and the heavy workload [17] are the most impacting factors associated with the occurrence of burnout. Lack of meaning of everyday work contributes to the moral distress of caregivers [2, 11, 21].

18.2 Consequences of Psychological Impairment Among ICU Caregivers

18.2.1 Why It Is Important to Take Care of the Caregivers

There are two essential reasons why caregivers should be taken cared of: one regards the quality of care and the second is managerial.

18.2.1.1 Quality of Care

The ICU caregivers need to be in a good mental health to be able to deliver a high quality of healthcare for the patients. In contrast, when overwhelmed by stress and burned out, they are prone to lose their sensitivity toward the emotion of patients, relatives, or colleagues [22] and may become uninterested by the situation. The doctors in burnout confess that they changed their practice or attitudes toward patients [3]. For example, they would discharge patients to make the service "manageable," order restraints on agitated patient

without evaluating him/her, and not pay attention to the personal impact of an illness on patient, letting them feel becoming less humane. Under stress, they tended to install limitation of therapy earlier than usual [23]. When the physicians are unwell, the performance of their care can decrease and be suboptimal [7, 24]. They confess that they would decide early limitation of therapy when submitted to stress [23].

18.2.1.2 Managerial Concerns

Safety of the Caregivers

Physicians under heavy workload suffer from fatigue and are more at risk of self-injuries [25], and extended work shifts increase the probability of car crashes on the way back home [26]. Both risks can lead to absence from work. Fatigue can decrease the concentration of faculty, eventually leading to medication error [27].

Burnout is also recognized to be associated with other mental ill-being such as sleep disruption, irritability, cognitive troubles, libido disorders, and depressive symptoms [6].

All these elements may converge into a vicious circle of bad feeling among the caregivers and entertain the psychological burden.

Caregivers suffering of burnout are more prone to depression [24].

Consequences of Burnout on the Patients and the Service

Professionals subject to burnout tend to abandon their task, regress toward ancillary habits, communicate badly, and show disorganization in their teamwork. The ensuing risks are conflicts and errors [28]. Such behavioural deterioration of the personal impacts on the organization of a service increases the delay of action, decreases the performance, and increases absenteeism and the turnover of the staff that is difficult to recruit. Moreover, nurses unsatisfied of their job and in burnout perform less well and fail to rescue promptly, increasing the mortality of patients [15].

Shortage of Caregivers

Professionals suffering from psychological impairment such as burnout want to leave their job [2, 13, 29]. This is a real concern since the shortage of ICU professional is a real threat for the quality of care of patients. This shortage was announced long ago [30], and present analysis by the national centre for health workforce analysis [31] seems to indicate that, in the USA, the demand in ICU caregivers will be fulfilled. The prediction in other countries is unknown.

18.3 How to Diagnose Mental Distress in an ICU Team

The answer resides in the approach that the service manager would like to install in his/her service. Indeed, as in the care of patients in critical care, monitoring itself cannot achieve any result, any improvement for the patient.

However, monitoring is necessary to detect the problem, and the deviation from the normal ranges may raise the alarm and trigger a corrective action.

Monitoring psychological impairment among caregivers requires a real commitment from the managers and some manpower.

The tools to measure the degree of burnout [22], PTSD [11], compassion fatigue [12], or moral distress [2] do exist and are reported elsewhere. All these tools are questionnaires that can be distributed to the caregivers who will be invited to fill them. The challenges in ICUs are time and method. The numerous questions with regard to such survey are as follows:

- Who will be installing the survey?
- On papers or on a web site?
- At what frequency?
- To all the caregivers? To selected caregivers?
- Who will collect the answers?
- Who will analyse the results?
- At what response rate the answers would be credible?
- How to give the feedback to the caregivers?
- Who will seek for the potential corrective actions?
- Who will decide of the one to be installed?
- Who will implement the corrective measure?

As demonstrated, this is a true work that should be recognized as such. This means that the heads of the service should be aware that such enterprise needs resources, time of dedicated personal in particular. Because of the time and energy required for this enterprise, it seems unreasonable to test all possible impairments, and the choice of the one to be followed should be made carefully.

Considering that monitoring can be automatized, a long-term follow-up of the mental health of the caregivers would be easier.

This type of project can refer to a quality improvement program with the approved methodology that has been proven efficient [32]. The most important aspect of such program is the continuous improvement of a structure or system with the PDCA circle that integrates the results of the monitoring into corrective actions (Fig. 18.1).

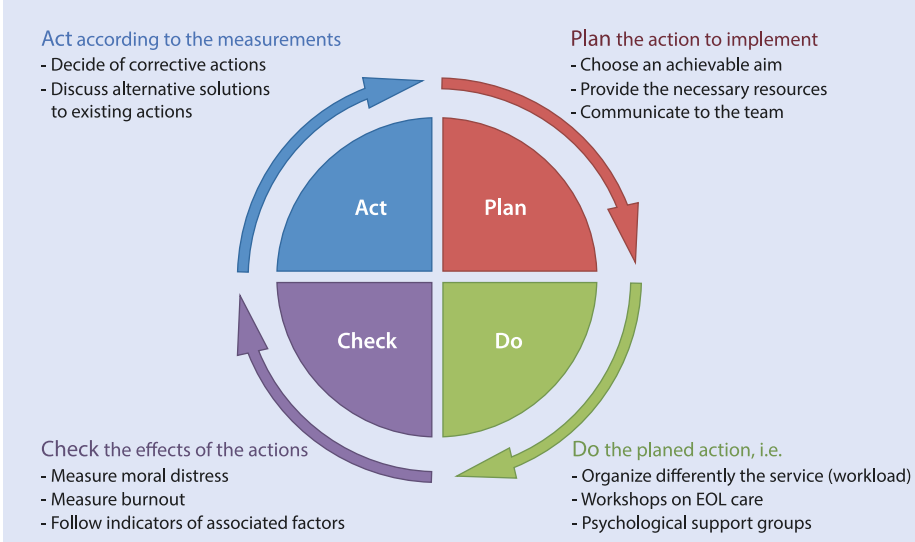


Fig. 18.1 PDCA circle

18.4 How to Prevent/Treat the Problem

Among the different known factors associated with the psychological impairment of ICU caregivers, some are inherent to the type of service and can hardly be modified. Indeed, the heavy workload and the unpredictable rush of patients with their dreadful history cannot be prevented.

In contrast, many of them, belonging to the human factors, can be worked out.

Unfortunately, there is no evidence of efficient preventing measure or treatment of psychological impairment of ICU caregivers.

18.4.1 The Modifiable Factors and Potential Targets for Improvement

The numerous works that investigated the psychological burden of ICU caregivers report the difficulties with regard to the relationships between caregivers themselves and the patient and/or family members.

The known factors of conflicts that were well described in the CONFLICUS study [20] are similar to the factors related to burnout: job strain, workload, inadequate communication, and end-of-life care. In answer to these human difficulties, it seems reasonably appropriate to think of solutions that take the humane dimensions in account.

Many potential solutions were proposed on a theoretical basis.

18.4.1.1 Team Building

Because of the special type of work, night and days for 7/7 days throughout the year, the complexity and burden of the cases, and the turnover of all caregivers, nurses, nurse assistants, and physicians, the ICU is an unfavourable milieu for the development of a team spirit. However, precisely because of all these barriers, effort for team building should be reinforced in this particular environment.

Team building can decrease risks of interprofessional conflicts and may eventually improve the relationships of patients and family members and patients' outcome, decreasing the causes which lead the caregivers to burnout [33].

18.4.1.2 Communication

A major challenge in the ICU is communication. Indeed, personnel under stress confronted with patients and family members under high pressure are natural ingredients for communication errors including aggressiveness and verbal abuse.

It is noteworthy that nurses complain of physicians' language, whereas these latter think that they are performing well with regard to communication. Communication around end-of-life decision is particularly difficult and can be a source of tension among the team [34].

In contrast, training in communication can help the ICU caregivers to take better decisions. In the work of Lilly, it allowed to better discern patients who might benefit of ICU from those who will be dying anyway [35].

18.4.1.3 Training in Ethics, Palliative, and End-of-Life Care

Deaths and end-of-life care are now part of the everyday practice of critical care. However, and because the ICU professionals do not choose this profession, that is to take care of dying patients, this part of the ICU mission might be a source of difficulty for them. Since end-of-life care and death of patients are part of the reasons of psychological suffering of ICU professional, it is essential that they would be given sufficient training and support in ethics, palliative, and end-of-life care. In particular, procedures that can help support colleagues caring for dying patients and facilitate rituals for the staff to recognize the death of patients should be installed. The nursing staff and medical rotation schedules should be adjusted to maximize continuity of care. The team should be encouraged to communicate regularly within the interdisciplinary team with regard to goals of care. A staff support group (facilitators) should be established, and the list of palliative care experts, that is pastoral care representatives, should be made easily available. These professionals could also teach and model end-of-life care to the ICU caregivers [36]. Palliative care is not only care after decision to withholding or withdrawing treatments but also includes explicit discussion about goals of care, patient- and family-centred decision-making, pain and symptom assessment and control, communication, and collaboration among the interdisciplinary team [37].

18.4.1.4 Admission Controls

Since the perception of inappropriate care can be burdensome for the ICU caregivers and lead to lack of sense of their profession [2], each admission into the ICU should be watched carefully. However, even the critical care physicians disagree on the justification of use of ICU for end of life [38]. The "Contra" protagonists argue that patients should not be submitted to aggressive but unnecessary technical measures. To note, in the USA, a fifth of US residents receive ICU care at EOL, and a fourth of the total healthcare expenditure is spent for the last year of life. In this context, use of ICU for the last days of life seems unreasonable. The "Pro" protagonists argue that it is impossible to determine in advance when the last year of life started, whether the present admission is due to an acute but reversible deterioration or a sign of downhill for the patient. We all know that acute event leading to ICU changes the prognosis of chronic disease. However, patients, especially elderly patients [39], and family members are not aware of this reality and process the potential changes of the future quite differently. Many family members hope that the patient would recover and are unaware of the suffering that they might impose to their beloved. Moreover, the sufferings of family caregivers who care for patients can be recognized after an ICU stay, whereas the family members continue to be unaware of such burden when they take the decision of pursuing treatments at any cost during the patients' ICU stay [40].

Finally, since ICU professionals became expert of pain control and palliative care, some would argue that ICU is the best place to die. This is without considering the burden of the ICU professionals and cost.

18.4.1.5 Psychological Support

Since there is now good evidence that ICU caregivers suffer psychologically, it seems reasonable to think that these professionals should benefit of some kind of support. However, no proven method of psychological support has been proposed [41]. The task of demon-

strating the potential benefit of such procedure is difficult. Indeed, in a single randomized controlled trial that we lead, we tested the impact of group support using two psychologists for ICU nurses. This 9-month project could not show a significant improvement of the burnout of the treated nurses for many organizational reasons among which 40% of caregivers had changed throughout the study period. There was a decrease in the burnout scores in the whole ICU team ("personal unpublished data").

More studies should be lead in order to assess the way to implement psychological support for ICU caregivers. Team supervision by a skilled psychiatrist or the presence of a psychologist or psychiatrist in the unit, which is implicated in the everyday life of the caregivers, is an example that should be explored in the context.

18.4.1.6 Hints for Management

There is probably no single preventive or therapeutic mean for the psychological impairment of ICU caregivers. However, recent advances in management and studies in other fields of medicine lead to the hope that some of the approaches might work in ICU too.

One important condition is the deep belief and commitment of the heads of ICU services that the psychological wellness of the caregivers is an inescapable priority in the management of their services, since it conditions the care for patients and family members.

The quality of care provided is essential in that it will determine not only their survival in ICUs but also the quality of life thereafter.

Also, we may not want to wait until we get scientific evidence before moving toward to care for ICU caregivers. Indeed, trials in our environment are difficult and may not reflect reality. Qualitative type of studies should also be considered to move forward.

A multimodal approach might include the following:

- Constitution of psychological support groups [42, 43]
- Education and development of mindfulness [44, 45]
- Team building [33]
- Self-help intervention [46]
- Therapeutic alliance [47]

Conclusions

ICU caregivers are at high risk of developing psychological impairment as shown in this chapter.

Since their psychological welfare impacts on their behaviour including their human ability to support patients and family members, everything should be done to protect ICU caregivers. The present state of knowledge does not allow determining a single recognized way to support this personal in the very special environment of ICU. However, there is no time to wait for the results of studies to start to take care of the ICU caregivers.

Take Home Messages

- ICU caregivers including physicians, nurses, and nurse assistants are at high risk of psychological impairment
- The psychological impairment of these professionals is directly related to the type of care that they are providing
  - The ICU environment is aggressive
  - The ICU patients' and families' suffering is burdensome.
  - Death is ubiquitous in ICU
- The psychological well-being of the caregivers impacts on the survival and quality of life of the patients
- Heads of ICUs should be aware of the necessary care of their personal
- A multimodal management approaches might be interesting
  - Team building
  - Education on communication
  - Education on ethics, palliative and end-of-life care
  - Psychological support
- Some promising future approaches are
  - Mindfulness
  - Development of resilience

» Not everything that can be counted counts, and not everything that counts can be counted. –Albert Einstein

References

1. Merlani P, Verdon M, Businger A, Domenighetti G, Pargger H, Ricou B. Burnout in ICU caregivers: a multicenter study of factors associated to centers. Am J Respir Crit Care Med. 2011;184(10):1140–6.
2. Piers RD, Azoulay E, Ricou B, Dekeyser Ganz F, Decruyenaere J, Max A, Michalsen A, Maia PA, Owczuk R, Rubulotta F, et al. Perceptions of appropriateness of care among European and Israeli intensive care unit nurses and physicians. JAMA. 2011;306(24):2694–703.
3. Shanafelt TD, Bradley KA, Wipf JE, Back AL. Burnout and self-reported patient care in an internal medicine residency program. Ann Intern Med. 2002;136(5):358–67.
4. Shanafelt TD, Balch CM, Bechamps GJ, Russell T, Dyrbye L, Satele D, Collicott P, Novotny PJ, Sloan J, Freischlag JA. Burnout and career satisfaction among American surgeons. Ann Surg. 2009;250(3):463–71.
5. Goehring C, Bouvier Gallacchi M, Kunzi B, Bovier P. Psychosocial and professional characteristics of burnout in Swiss primary care practitioners: a cross-sectional survey. Swiss Med Wkly. 2005;135(7–8):101–8.
6. Poncet MC, Toullic P, Papazian L, Kentish-Barnes N, Timsit JF, Pochard F, Chevret S, Schlemmer B, Azoulay E. Burnout syndrome in critical care nursing staff. Am J Respir Crit Care Med. 2007;175(7):698–704.
7. Embriaco N, Hraiech S, Azoulay E, Baumstarck-Barrau K, Forel JM, Kentish-Barnes N, Pochard F, Loundou A, Roch A, Papazian L. Symptoms of depression in ICU physicians. Ann Intensive Care. 2012;2(1):34.
8. Levy MM. Caring for the caregiver. Crit Care Clin. 2004;20(3):541–7, xi

9. Desarmenien M, Blanchard-Courtois AL, Ricou B. The chronic critical illness: a new disease in intensive care. Swiss Med Wkly. 2016;146:w14336.
10. Lamas DJ, Owens RL, Nace RN, Massaro AF, Pertsch NJ, Gass J, Bernacki RE, Block SD. Opening the door: the experience of chronic critical illness in a long-term acute care hospital. Crit Care Med. 2017;45(4):e357–62.
11. Mealer ML, Shelton A, Berg B, Rothbaum B, Moss M. Increased prevalence of post-traumatic stress disorder symptoms in critical care nurses. Am J Respir Crit Care Med. 2007;175(7):693–7.
12. Hinderer KA, VonRueden KT, Friedmann E, McQuillan KA, Gilmore R, Kramer B, Murray M. Burnout, compassion fatigue, compassion satisfaction, and secondary traumatic stress in trauma nurses. J Trauma Nurs. 2014;21(4):160–9.
13. Embriaco N, Azoulay E, Barrau K, Kentish N, Pochard F, Loundou A, Papazian L. High level of burnout in intensivists: prevalence and associated factors. Am J Respir Crit Care Med. 2007;175(7):686–92.
14. Verdon M, Merlani P, Perneger T, Ricou B. Burnout in a surgical ICU team. Intensive Care Med. 2008;34(1):152–6.
15. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 2002;288(16):1987–93.
16. Coomber S, Todd C, Park G, Baxter P, Firth-Cozens J, Shore S. Stress in UK intensive care unit doctors. Br J Anaesth. 2002;89(6):873–81.
17. Wall S, Austin WJ, Garros D. Organizational influences on health professionals' experiences of moral distress in PICUs. HEC Forum. 2016;28(1):53–67.
18. Shanafelt TD. Enhancing meaning in work: a prescription for preventing physician burnout and promoting patient-centered care. JAMA. 2009;302(12):1338–40.
19. Teixeira C, Ribeiro O, Fonseca AM, Carvalho AS. Ethical decision making in intensive care units: a burnout risk factor? Results from a multicentre study conducted with physicians and nurses. J Med Ethics. 2013 (February 13, 2013 as https://doi.org/10.1136/medethics-2012-100619).
20. Azoulay E, Timsit JF, Sprung CL, Soares M, Rusinova K, Lafabrie A, Abizanda R, Svantesson M, Rubulotta F, Ricou B, et al. Prevalence and factors of intensive care unit conflicts: the conflicus study. Am J Respir Crit Care Med. 2009;180(9):853–60.
21. Moss M, Good VS, Gozal D, Kleinpell R, Sessler CN. An official critical care societies collaborative statement-burnout syndrome in critical care health-care professionals: a call for action. Chest. 2016;150(1):17–26.
22. Maslach C. Burnout: the cost of caring. New York: Prentice Hall; 1982.
23. Hua M, Halpern SD, Gabler NB, Wunsch H. Effect of ICU strain on timing of limitations in life-sustaining therapy and on death. Intensive Care Med. 2016;42(6):987–94.
24. Wallace JE, Lemaire JB, Ghali WA. Physician wellness: a missing quality indicator. Lancet. 2009;374(9702):1714–21.
25. Ayas NT, Barger LK, Cade BE, Hashimoto DM, Rosner B, Cronin JW, Speizer FE, Czeisler CA. Extended work duration and the risk of self-reported percutaneous injuries in interns. JAMA. 2006;296(9):1055–62.
26. Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, Czeisler CA, Harvard Work Hours H, Safety G. Extended work shifts and the risk of motor vehicle crashes among interns. N Engl J Med. 2005;352(2):125–34.
27. Fahrenkopf AM, Sectish TC, Barger LK, Sharek PJ, Lewin D, Chiang VW, Edwards S, Wiedermann BL, Landrigan CP. Rates of medication errors among depressed and burnt out residents: prospective cohort study. BMJ. 2008;336(7642):488–91.
28. Vahey DC, Aiken LH, Sloane DM, Clarke SP, Vargas D. Nurse burnout and patient satisfaction. Med Care. 2004;42(2 Suppl):II57–66.
29. Heinen MM, van Achterberg T, Schwendimann R, Zander B, Matthews A, Kozka M, Ensio A, Sjetne IS, Moreno Casbas T, Ball J, et al. Nurses' intention to leave their profession: a cross sectional observational study in 10 European countries. Int J Nurs Stud. 2012;50(2):174–84.
30. Halpern NA, Pastores SM, Thaler HT, Greenstein RJ. Changes in critical care beds and occupancy in the United States 1985–2000: differences attributable to hospital size. Crit Care Med. 2006;34(8):2105–12.
31. HSRA. Health workforce projections: critical care physicians and nurse practitioners; 2017.
32. Staines A, Thor J, Robert G. Sustaining improvement? The 20-year Jonkoping quality improvement program revisited. Qual Manag Health Care. 2015;24(1):21–37.
33. Reader TW, Flin R, Mearns K, Cuthbertson BH. Developing a team performance framework for the intensive care unit. Crit Care Med. 2009;37(5):1787–93.

34. Cohen S, Sprung C, Sjokvist P, Lippert A, Ricou B, Baras M, Hovilehto S, Maia P, Phelan D, Reinhart K, et al. Communication of end-of-life decisions in European intensive care units. Intensive Care Med. 2005;31(9):1215–21.
35. Lilly CM, Sonna LA, Haley KJ, Massaro AF. Intensive communication: four-year follow-up from a clinical practice study. Crit Care Med. 2003;31(5 Suppl):S394–9.
36. Clarke EB, Curtis JR, Luce JM, Levy M, Danis M, Nelson J, Solomon MZ. Quality indicators for end-of-life care in the intensive care unit. Crit Care Med. 2003;31(9):2255–62.
37. Curtis JR. Caring for patients with critical illness and their families: the value of the integrated clinical team. Respir Care. 2008;53(4):480–7.
38. Angus DC, Truog RD. Toward better ICU use at the end of life. JAMA. 2016;315(3):255–6.
39. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868): 752–62.
40. Cameron JI, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, Friedrich JO, Mehta S, Lamontagne F, Levasseur M, et al. One-year outcomes in caregivers of critically ill patients. N Engl J Med. 2016;374(19):1831–41.
41. Teasdale K, Brocklehurst N, Thom N. Clinical supervision and support for nurses: an evaluation study. J Adv Nurs. 2001;33(2):216–24.
42. Arneson H, Ekberg K. Evaluation of empowerment processes in a workplace health promotion intervention based on learning in Sweden. Health Promot Int. 2005;20(4):351–9.
43. Scates CL, S. ; Sutherland, J. Supporting clinical teams through group reflective practice. In: 11th congress of European association of palliative care. Vienna. May 2009.
44. Krasner MS, Epstein RM, Beckman H, Suchman AL, Chapman B, Mooney CJ, Quill TE. Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. JAMA. 2009;302(12):1284–93.
45. Steinberg BA, Klatt M, Duchemin AM. Feasibility of a mindfulness-based intervention for surgical intensive care unit personnel. Am J Crit Care. 2016;26(1):10–8.
46. Geraedts AS, Kleiboer AM, Wiezer NM, van Mechelen W, Cuijpers P. Short-term effects of a web-based guided self-help intervention for employees with depressive symptoms: randomized controlled trial. J Med Internet Res. 2014;16(5):e121.
47. Huff NG, Nadig N, Ford DW, Cox CE. Therapeutic alliance between the caregivers of critical illness survivors and intensive care unit clinicians. Ann Am Thorac Soc. 2015;12(11):1646–53.

Rehabilitation

Contents

Modalities for Physical Rehabilitation

Rik Gosselink, M. Van Hollebeke, B. Clerckx, and D. Langer

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_19

Learning Objectives

- To understand the various steps in the assessment and treatment of physical deconditioning of the critically ill patients in the acute and chronic phase of their recovery
- To understand the different modalities of physical rehabilitation and their effectiveness in acute and chronic critical illness
- To understand the multidisciplinary approach of physical rehabilitation, specifically in the acute critically ill patient

19.1 Introduction

The progress of intensive care medicine has dramatically improved survival of critically ill patients, especially in patients with acute respiratory distress syndrome (ARDS) and sepsis [1, 2]. However, this improved survival is often associated with general deconditioning, muscle weakness, prolonged mechanical ventilation, dyspnoea, depression, anxiety, and reduced health-related quality of life after intensive care unit (ICU) discharge [3, 4]. Deconditioning and specifically muscle weakness have a key role in impaired functional status after ICU stay [5, 6]. Bed rest and limited mobility during critical illness result in profound physical deconditioning and dysfunction of the respiratory, cardiovascular, musculoskeletal, neurological, renal, and endocrine systems [7]. These effects can be exacerbated by inflammation and pharmacological agents, such as corticosteroids, neuromuscular blockers, and antibiotics associated with critical illness and its treatment. The prevalence of skeletal muscle weakness in the intensive care unit (ICU-acquired weakness) varies up to 50%. Skeletal muscle wasting appears to be the highest during the first 2–3 weeks of ICU stay [8–11] and is associated with weaning failure, ICU and hospital length of stay, and increased 1-year mortality [5, 12].

The abovementioned changes in functional performance as well as limb muscle and respiratory muscle function indicate the need for assessment and measures to prevent deconditioning and loss of physical function *during* and *after* ICU stay [13]. It is important to prevent or attenuate muscle deconditioning as early as possible in patients with prolonged critical illness and expected extended bed rest. Over the last decade, increasing scientific and clinical interest and evidence have given support to a safe and early physical activity and mobilisation approach toward the critically ill patient by ICU team members [14, 15]. Although early mobilisation and physical activity have been shown to be effective on short-term outcomes in several studies [16–19], other studies were unable to show effectiveness on long-term outcomes [20, 21]. Several reasons, such as differences in populations, interventions, comparators, and outcomes, might account for these different findings [22].

The post-ICU discharge recovery period has been relatively ignored. Several longitudinal observational follow-up studies of survivors of critical illness have shown profound impairments including not only physical but also psychological, cognitive, and health-related quality of life [23]. Given the observed residual impairments in physical function, there is rationale for the ongoing delivery of exercise-based rehabilitation interventions in the post-ICU discharge period. However, the outcome of post-discharge rehabilitation including exercise training is at least unresolved [24]. Appropriate assessment and supervised exercise training following the guidelines from the American College of Sports Medicine [ACSM] [25], lacking in most of the studies so far, are probably important factors in the effectiveness of post-discharge rehabilitation.

19.2 Assessment

The detrimental physiological effects of recumbency and restricted mobility on all systems and the benefits of being upright and moving have been widely reported. However, issues related to early physical activity and mobilisation of patients in the ICU as a therapeutic option including *safety*, *dose*, and *implementation* have only recently been a shared focus of interest to interdisciplinary teams practising in the ICU [17, 26–28]. Accurate assessment of cardiorespiratory reserve and rigorous screening for other factors that could preclude early mobilisation is of paramount importance [29]. In addition to assessment of the safety and readiness of the patient for exercise and physical activity, specific measures of function (e.g. muscle strength, joint mobility), functional status (e.g. outcomes for functional performance such as the Functional Independence Measure [FIM], Berg Balance Scale [BBS], Functional Ambulation Categories [FAC], Physical Function ICU Test [PFIT], Chelsea Critical Care Physical Assessment [CPAx]), and quality of life (e.g. Medical Outcome Survey Short Form 36 [SF-36], disease-specific questionnaires) must be considered (► Box 19.1). See overview [30, 31].

Box 19.1 Assessment of the (Post) Critically Ill Patient

Cooperation – level of confusion, agitation, sedation, and consciousness
- Glasgow Coma Scale (GCS)
- Confusion Assessment for the ICU (CAM ICU)
- Richmond Agitation and Sedation Scale (RASS)
- Standardised five questions

Joint mobility
- Active and passive range of motion

Respiratory and Limb Muscle function
- Medical Research Council 0–5 scale/Medical Research Council sum score
- Hand held dynamometry
- Muscle twitch stimulation force
- Muscle thickness with ultrasonography
- Maximal inspiratory and expiratory pressure

Mobility – functional status
- Barthel Index
- Functional Independence Measure
- Katz ADL Scale
- Berg Balance Scale
- Functional ambulation categories
- 4-meter gait speed test
- Physical Function ICU Test (PFIT)

Quality of Life
- SF-36
- EuroQol

Exercise testing (post ICU)
- 6-min walking distance
- Shuttle walk test
- Incremental cycle ergometer test

19.3 Modalities for Physical Rehabilitation

19.3.1 Critically Ill Patients

Acutely ill, uncooperative patients are treated with modalities that do not need cooperation of the patient and will not put stress on their vulnerable cardiorespiratory system, such as passive range of motion, muscle stretching, splinting, body positioning, passive cycling with a bed cycle, or electrical muscle stimulation. On the other hand, the stable cooperative patient, beyond the acute illness phase but still on mechanical ventilation, will be able to be mobilised on the edge of the bed, to do transfers to a chair, perform resistance muscle training or active cycling with a bed cycle or chair cycle, and walk with or without assistance. A flow diagram was developed by Gosselink et al. [32] based on the scheme of Morris et al. [17] (Fig. 19.1). The flow diagram has face validity and is an example of such a step-up approach. The following paragraphs will deal with modalities of exercise training with progressive intensity and increasing need of cooperation of the patient.

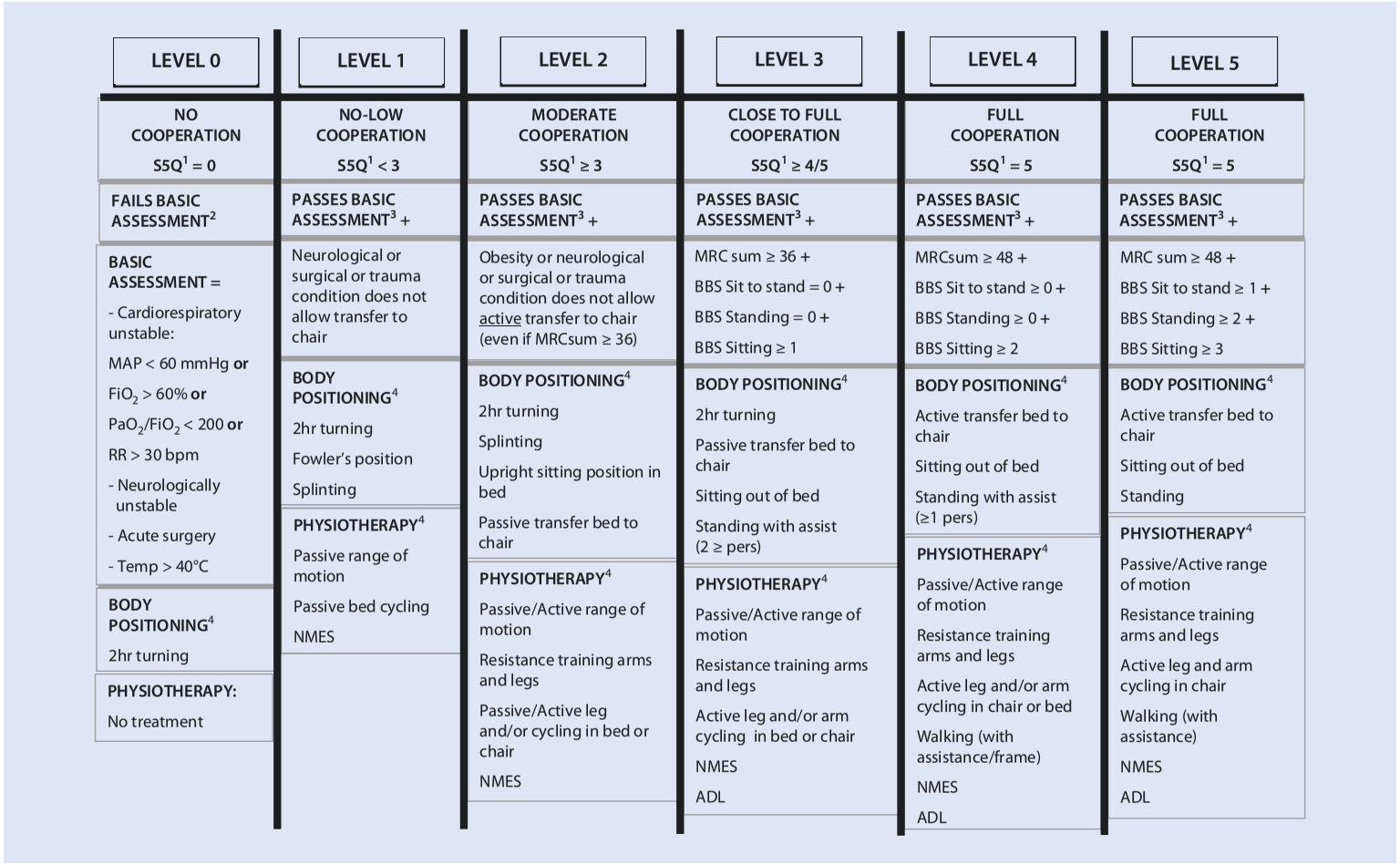
19.3.1.1 The Uncooperative Critically Ill Patient

Body positioning has been used prescriptively to remediate oxygen transport deficits such as impaired gas exchange by altering the distribution of ventilation (V) and perfusion (Q), V/Q matching, airway closure, work of breathing and cardiac workload, as well as mucus transport (postural drainage). To simulate the normal perturbations that the human body experiences in health, the patient who is critically ill needs to be positioned more upright

Fig. 19.1 "Start to move" – protocol Leuven: step-up approach of progressive mobilisation and physical activity programme. (Adapted from Gosselink et al. [32]). [1]S5Q: response to five standardised questions for cooperation: Open and close your eyes; look at me; open your mouth and stick out your tongue; shake yes and no (nod your head); I will count to 5, frown your eyebrows afterwards. [2]: FAILS when at least 1 risk factor is present. [3]: If basic assessment failed, decrease to level 0. [4]: Safety – each activity should be deferred if severe adverse events (cv., resp. and subject. intolerance) occur during the intervention. MRC (Medical Research Council) muscle strength sum scale (0–60), BBS: Berg Balance Score
Sitting to standing
- 4 able to stand without using hands and stabilise independently
- 3 able to stand independently using hands
- 2 able to stand using hands after several tries
- 1 needs minimal aid to stand or stabilise
- 0 needs moderate or maximal assist to stand

Standing unsupported
- 4 able to stand safely for 2 min
- 3 able to stand for 2 min with supervision
- 2 able to stand for 30 s unsupported
- 1 needs several tries to stand for 30 s unsupported
- 0 unable to stand for 30 s unsupported

Sitting with back unsupported but feet supported on the floor or on a stool
- 4 able to sit safely and securely for 2 min
- 3 able to sit for 2 min under supervision
- 2 able to able to sit for 30 s
- 1 able to sit for 10 s
- 0 unable to sit without support for 10 s



LEVEL 0	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5
NO COOPERATION S5Q[1] = 0	**NO-LOW COOPERATION** S5Q[1] < 3	**MODERATE COOPERATION** S5Q[1] ≥ 3	**CLOSE TO FULL COOPERATION** S5Q[1] ≥ 4/5	**FULL COOPERATION** S5Q[1] = 5	**FULL COOPERATION** S5Q[1] = 5
FAILS BASIC ASSESSMENT[2]	**PASSES BASIC ASSESSMENT**[3] +	**PASSES BASIC ASSESSMENT**[3] +	**PASSES BASIC ASSESSMENT**[3] +	**PASSES BASIC ASSESSMENT**[3] +	**PASSES BASIC ASSESSMENT**[3] +
BASIC ASSESSMENT = - Cardiorespiratory unstable: MAP < 60 mmHg **or** FiO_2 > 60% **or** PaO_2/FiO_2 < 200 **or** RR > 30 bpm - Neurologically unstable - Acute surgery - Temp > 40°C	Neurological or surgical or trauma condition does not allow transfer to chair	Obesity or neurological or surgical or trauma condition does not allow active transfer to chair (even if MRCsum ≥ 36)	MRC sum ≥ 36 + BBS Sit to stand = 0 + BBS Standing = 0 + BBS Sitting ≥ 1	MRCsum ≥ 48 + BBS Sit to stand ≥ 0 + BBS Standing ≥ 0 + BBS Sitting ≥ 2	MRC sum ≥ 48 + BBS Sit to stand ≥ 1 + BBS Standing ≥ 2 + BBS Sitting ≥ 3
BODY POSITIONING[4] 2hr turning	**BODY POSITIONING**[4] 2hr turning Fowler's position Splinting	**BODY POSITIONING**[4] 2hr turning Splinting Upright sitting position in bed Passive transfer bed to chair	**BODY POSITIONING**[4] 2hr turning Passive transfer bed to chair Sitting out of bed Standing with assist (2 ≥ pers)	**BODY POSITIONING**[4] Active transfer bed to chair Sitting out of bed Standing with assist (≥1 pers)	**BODY POSITIONING**[4] Active transfer bed to chair Sitting out of bed Standing
PHYSIOTHERAPY: No treatment	**PHYSIOTHERAPY**[4] Passive range of motion Passive bed cycling NMES	**PHYSIOTHERAPY**[4] Passive/Active range of motion Resistance training arms and legs Passive/Active leg and/or cycling in bed or chair NMES	**PHYSIOTHERAPY**[4] Passive/Active range of motion Resistance training arms and legs Active leg and/or arm cycling in bed or chair NMES ADL	**PHYSIOTHERAPY**[4] Passive/Active range of motion Resistance training arms and legs Active leg and/or arm cycling in chair or bed Walking (with assistance/frame) NMES ADL	**PHYSIOTHERAPY**[4] Passive/Active range of motion Resistance training arms and legs Active leg and arm cycling in chair Walking (with assistance) NMES ADL

(well supported), or rotated when recumbent. These perturbations need to be scheduled frequently to avoid the adverse effects of prolonged static positioning on respiratory, cardiac, and circulatory function. The potent and direct physiological effects of changing body position on oxygen transport and oxygenation are exploited when mobilisation is contraindicated. This evidence comes primarily from the space science literature in which bed rest has been used as a model of weightlessness. Other indications for active and passive positioning include the management of soft tissue contracture, protection of flaccid limbs and lax joints, nerve impingement, and skin breakdown. Although a specific body position may be indicated for a patient, varied positions and frequent body position changes, particularly extreme body positions, are based on the assessment findings. The efficacy of 2-hourly patient rotation, which is common in clinical practice, has not been verified scientifically. Medically unstable patients who require a rotating or kinetic bed benefit from continuous side-to-side perturbation, which supports the hypothesis that patients may benefit from frequent and extreme position changes rather than fixed, prolonged periods in given positions [33]. Bed design features in critical care should include hip and knee breaks so that the patient can approximate upright sitting as much as can be tolerated. Heavy care patients such as those who are sedated, heavy, or overweight may need chairs with greater support such as stretcher chairs. Lifts may be needed to change a patient's position safely.

Passive stretching or *range of motion exercise* may have a particularly important role in the management of patients who are unable to move spontaneously. Studies in healthy subjects have shown that passive stretching decreases stiffness and increases extensibility of the muscle. Evidence for using continuous dynamic stretching (and counterbalancing the 'silencing' of the muscle in critically ill patients [34]) is based on the observation in patients with critical illness subjected to prolonged inactivity. Nine hours of continuous passive motion per day reduced the loss of muscle strength, muscle atrophy, and protein loss in critically ill patients [35, 36].

Splinting may be indicated for patients who cannot be actively mobilised and have high risk of soft tissue contracture, such as following severe burns, trauma, and some neurological conditions. Splinting of the periarticular structures in the stretched position for more than half an hour per day was shown to have a beneficial effect on the range of motion (ROM) in an animal model [37]. In burns patients, fixing the position of joints reduced muscle and skin contraction [38], while in patients with neurological dysfunction, splinting may reduce muscle tone [39].

Neuromuscular electrical stimulation (NMES) has been used in patients unable to perform voluntary muscle contractions, to prevent disuse muscle atrophy. Daily NMES for at least 1 h during an immobilisation period reduced the decrease in cross-sectional area of the quadriceps and enhanced normal muscle protein synthesis in patients with lower-limb fractures and cast immobilisation [40]. For patients in the ICU who are not able to move actively, NMES was also introduced to preserve muscle strength and muscle mass. Although the trend of the effectiveness on muscle strength and muscle mass is positive, results of the studies are conflicting [41, 42]. Several reasons may account for these findings, such as patient characteristics (sepsis, oedema, use of vasopressives [43]), timing of NMES related to ICU admission, protocol for stimulation (devices, stimulation duration, and frequency), and varying methodology for assessment of muscle function (muscle mass, strength). NMES of the quadriceps, in addition to active limb mobilisation, enhanced muscle strength and hastened independent transfer from bed to chair in patients with prolonged critical illness [44].

The application of exercise training in the early phase of ICU admission is often more complicated due to lack of cooperation and the clinical status of the patient. Technological

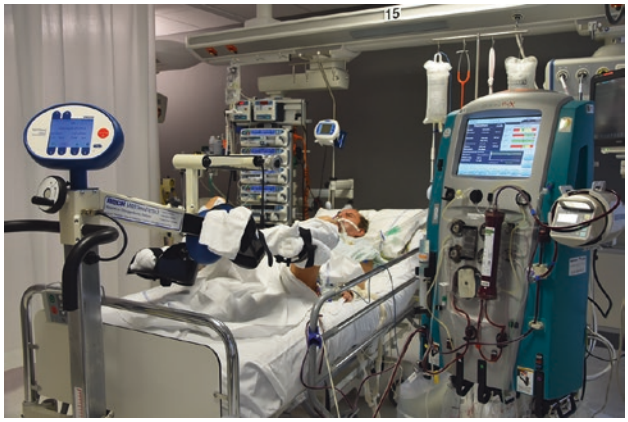


Fig. 19.2 Bed cycling in critically ill patient on mechanical ventilation and renal dialysis

development resulted in a *bed cycle ergometer* for (active or passive) leg cycling during bed rest (Fig. 19.2). The application of this training modality has been shown to be a safe and feasible exercise tool in (neurological) ICU patients [18, 45, 46]. The bedside cycle ergometer enables a prolonged continuous mobilisation, allowing rigorous control of exercise intensity and duration. A randomised controlled trial of early application of daily bedside leg cycling in critically ill patients showed improved functional status, muscle function, and exercise performance at hospital discharge compared with patients receiving standard physiotherapy without leg cycling [18].

19.3.1.2 The Cooperative Critically Ill Patient

Mobilisation refers to physical activity sufficient to elicit acute physiological responses such as increased ventilation, central and peripheral perfusion, circulation, muscle metabolism, and alertness. Strategies – in order of intensity – include sitting on the edge of the bed, standing, stepping in place, turning from side to side in bed and transferring from bed to chair, and walking with or without support. The approach of early mobilisation has face validity, and it was shown that patients receiving early mobility therapy had reduced ICU and hospital stay, improved functional status at hospital discharge, shortened duration of delirium, and increased ventilator-free days [16, 17]. The team approach (doctor, nurse, physiotherapist, and occupational therapist) is an important and strong point in establishing an early ambulation programme [15, 47]. These early intervention attempts are, although challenging, specifically for patients still in need of supportive devices (mechanical ventilation, cardiac assists, extracorporeal membrane oxygenation) or unable to stand without support of personnel or standing aids, a worthwhile experience for the patient [17, 48]. The risk of adverse events during these interventions is very low [49].

Standing and walking frames enable the patient to mobilise safely with attachments for bags, lines, and leads that cannot be disconnected (Fig. 19.3). The arm support on a frame or rollator has been shown to increase ventilatory capacity in patients with severe chronic obstructive pulmonary disease [50]. The frame needs to be able to accommodate either a portable oxygen tank or a portable mechanical ventilator and seat, or a suitable trolley for equipment can be used. Not only walking and standing aids but also tilt tables enhance physiological responses [51] and enable early mobilisation of critically ill patients. Therefore, the tilt table may be used when the patient is unable to move his legs to counter-dependent fluid displacement and might be at risk of orthostatic intolerance. Abdominal belts applied in patients with spinal cord injury improve vital capacity and need to be

Fig. 19.3 Assisted transfer from bed to standing position of a critically ill patient on mechanical ventilation

carefully positioned to support, not restrict, respiration during mobilisation [52]. Transfer belts facilitate heavy lifts and protect both the patient and the physiotherapist or nurse. Noninvasive ventilation (NIV) during mobilisation may improve exercise tolerance for non-intubated patients, similar to that demonstrated in patients with stable chronic obstructive pulmonary disease [53]. In ventilated patients, the ventilator settings may require adjustment to the patient's needs (i.e. increased minute ventilation or FiO_2).

Aerobic training and muscle strengthening, in addition to routine mobilisation, improved walking distance more than mobilisation alone in patients with chronic critical illness on long-term mechanical ventilation [54, 55]. A randomised controlled trial showed that a 6-week upper- and lower-limb training programme improved limb muscle strength, ventilator-free time, and functional outcomes in patients requiring long-term mechanical ventilation compared to a control group [54]. These results are in line with a retrospective analysis of patients on long-term mechanical ventilation who participated in whole-body training and respiratory muscle training [56]. In patients recently weaned from mechanical ventilation, the addition of upper-limb exercise enhanced the effects of general mobilisation on exercise endurance performance and dyspnoea [57]. Low-resistance multiple repetitions of resistive muscle training, including the use of pulleys, elastic bands, and weight belts, can augment muscle mass and strength (Fig. 19.4). Sets of repetitions (3 sets of 8–10 repetitions at 50–70% of one repetition maximum [1RM]) within the patient's tolerance can be scheduled daily, commensurate with their goals.

The *chair cycle* (■ Fig. 19.5) and the *bed cycle* allow patients to perform an individualised exercise training programme. The intensity of cycling can be adjusted to the individual patient's capacity, ranging from passive cycling via assisted cycling to cycling against

Fig. 19.4 Resistance muscle training with elastic bands in a critically ill patient

Fig. 19.5 Chair cycling in a patient admitted to the ICU

increasing resistance. The prescription of exercise intensity, duration, and frequency is response-dependent rather than time-dependent and is based on clinical challenge tests, such as the response to a nursing or investigative procedure or to a specific mobilisation challenge. Exercise should be safely tolerated in any treatment session, and if the patient responds positively, greater intensity and duration can be applied. For acutely ill patients, frequent short sessions (analogous to interval training) allow greater recovery than the less frequent, longer sessions prescribed for patients with chronic stable conditions [58].

19.3.1.3 Clinical Implementation

The amount of rehabilitation performed in ICUs is often inadequate [59–61], and as a rule, rehabilitation is better organised in weaning centres or respiratory ICUs (RICUs) [27, 56]. Different (modifiable) barriers for mobilisation and rehabilitation were identified by nurses, physiotherapists, and physicians: limited (experienced) staff and supporting equipment, no protocol, no mobility culture, lack of planning and coordination, no 'champion' in the team, or 'standing bed rest' order [62, 63]. However, the risk of moving a critically ill patient should be weighed against the risk of immobility and recumbency, and when employed, it requires stringent monitoring to ensure that the mobilisation is instituted appropriately and safely [29]. Several strategies to improve the implementation of early mobilisation were suggested for patient-related, structural, procedural, and cultural barriers [63]. This will enable the ICU team, in a multidisciplinary and multiprofessional environment, to prioritise and identify aims and parameters of treatments, ensuring that these are both therapeutic (also in the long term) and safe [64].

19.3.1.4 Weaning and Respiratory Muscle Training

Twenty to thirty percent of patients fail liberation from mechanical ventilation and require a disproportionate amount of resources [65]. Several factors are likely to contribute to weaning failure including inadequate ventilatory drive, respiratory muscle weakness, respiratory muscle fatigue, increased work of breathing, airway and lung dysfunction, brain dysfunction, cardiac failure, and endocrine and metabolic dysfunctions [66]. The inability to breathe spontaneously relates to an imbalance between *load on* the respiratory muscles and the *capacity of* the respiratory muscles [67]. High rate of respiratory muscle effort (ratio of workload and muscle capacity (P_I/P_{Imax})) is a major cause of ventilator dependency and predicts the outcome of successful weaning [68]. Severe inspiratory muscle weakness (PImax: 13–25 cmH_2O) in mechanically ventilated patients is observed in 80% of patients with ICUAW [69]. The decline in transdiaphragmatic pressure is approximately 2–4% per day in the first weeks of ICU stay [11] and is associated with severe sepsis or severe shock [70, 71]. Since *in*activity contributes considerably to muscle atrophy, "mechanical silencing" has been identified as an important contributor to the loss of contractile properties [35]. A lower contractile activity of the diaphragm during mechanical ventilation was associated with further reduction of diaphragm thickness [72]. Additionally, patient-ventilator dyssynchrony and overloading the respiratory muscles during the weaning phase can also lead to prolonged weaning [73]. This observation supports the idea that well-balanced, intermittent loading of the respiratory muscles during the process of mechanical ventilation might be beneficial to prevent or ameliorate muscle atrophy. Indeed, modalities inducing (intermittent) loading of the respiratory muscles such as spontaneous breathing trials increase muscle strength [74], and early mobilisation has been shown to shorten the duration of mechanical ventilation [16]. Surprisingly, little attention has been given to specific interventions to enhance strength

Fig. 19.6 Inspiratory muscle training with feedback in a patient with difficult weaning from mechanical ventilation

and endurance of the respiratory muscles. Indeed, daily inspiratory muscle training with 6–8 contractions repeated in 3–4 series at moderate to high intensity was safe and improved both inspiratory muscle strength and weaning success in patients with difficult weaning [75, 76]. The studies performed so far on IMT in mechanically ventilated patients were heterogeneous with regard to specific inclusion criteria, training modalities, and outcomes evaluated. Not all studies specifically focused on patients with known weaning difficulties, and not all studies evaluated weaning-related outcomes. Timing of inclusion of patients was also not consistent between studies. Specifically, patients with known weaning difficulties seem more likely to benefit from an IMT intervention during mechanical ventilation [75]. In addition, most of those RCTs used a mechanical threshold-loading (MTL) device for IMT which might not offer the ideal loading characteristics in this specific setting. An alternative, potentially more optimal way of loading the respiratory muscles is tapered flow resistive loading (TFRL) IMT [77]. This isokinetic loading approach during TFRL is better adapted to the length-tension characteristics of the inspiratory muscles than the isotonic muscle loading applied during MTL. Consequently, TFRL results in a contraction that is performed at constant velocity (i.e. constant inspiratory flow rate). This characteristic and visual feedback on the screen will allow larger tidal volumes to be achieved during IMT (◘ Fig. 19.6). In analogy with data presented previously in patients with COPD, it is expected to result in better tolerance of higher training intensities with subsequent larger improvements in respiratory muscle function in comparison to MTL [78]. One of the challenges of IMT is that patients who might benefit from the intervention are oftentimes not sufficiently capable to collaborate during the training sessions.

19.3.2 Post Critically Ill Patients

The post-ICU discharge stages of recovery have been relatively ignored. Several longitudinal observational follow-up studies of survivors of critical illness have shown profound impairments not only in physical but also in psychological, cognitive, and health-related quality-of-life domains [23]. Given the residual impairments in physical function, there is a rationale for the ongoing delivery of exercise-based rehabilitation interventions. Although post-discharge rehabilitation was associated with a reduced risk of 10-year mortality [79], the outcome of exercise training programmes was unanswered [24]. Most of the evaluated

programmes consist of home-based programmes [80], guided by self-help rehabilitation manuals [81] and/or intermediate telephone calls [82]. A more recent partially supervised exercise training programme lasting only 6 weeks resulted in significant larger short-term improvements of role physical function, functional exercise performance, and self-efficacy and readiness to exercise compared to a control group [83]. The lack of supervised exercise training in most of these studies, ignoring the guidelines from the American College of Sports Medicine [25], is probably an important factor in the lack of effectiveness. The ACSM recommends a comprehensive programme of exercise including cardiorespiratory, resistance, flexibility, and neuromotor exercise of sufficient volume (intensity, duration, and frequency) for healthy adults of all ages (► Box 19.2) [25, 84]. Exercises performed in this manner have been reported to improve physical and mental health and/or fitness in healthy subjects and patient populations [25]. The exercise prescription is best adjusted according to individual responses because of the considerable individual variability in response to exercise. Basically, there is no reason why post-intensive care syndrome (PICS) patients, oftentimes suffering from (pre-existent) cardiopulmonary disease, would not be able to follow the same guidelines. This was concluded in a recent expert consensus statement [31]. Evaluation of participants, as practiced in cardiopulmonary rehabilitation, including exercise testing (► Box 19.1), allows screening of causes for exercise limitation (cardiovascular, respiratory, muscle weakness, or psychological impairment). Specifically, patients with PICS are suffering from muscle weakness as an important cause for exercise limitation [4]. Since there is considerable individual variability in the response to exercise, this information is important for the exercise prescription in an individualised training programme supervised by an experienced physical therapist or exercise physiologist. Finally, exercise is only beneficial if a person engages in it, and oftentimes (at least partly) supervised training is necessary to improve physical fitness in patient populations. To this end, focusing on individual preferences and enjoyment and incorporating health behaviour theory and behaviour change strategies into exercise counselling interventions and programmes can enhance adoption and short-term maintenance of regular exercise.

Take Home Messages

- Critical illness is associated with short- and long-term morbidity: muscle weakness, weaning failure, impaired functional status, and quality of life.
- (Early) physical activity and rehabilitation are key in the prevention, attenuation, or reversion of the deconditioning.
- A variety of evidence-based modalities for exercise training and early mobility may be applied, depending on the stage of critical illness, comorbid conditions, and cooperation of the patient.
- Physical rehabilitation includes a wide range of modalities including passive, active, and resistance exercises, aiming to improve whole body endurance, muscle strength, flexibility, and coordination to enhance functional performance. The guidelines of the American College of Sports Medicine provide an adequate framework also for the (post) critically ill patient population.
- Physical rehabilitation is teamwork and should be administered jointly with medical, physical therapy, and nursing staff. The physical therapist should be responsible for implementing mobilisation plans and exercise prescription and make recommendation for progression of these in conjunction with the other team members.

Box 19.2 Summary of American College of Sports Medicine's Physical Activity Recommendations for Older Adults. Adapted from: Garber et al. [25] and Pascatello et al. [84]

Cardiorespiratory	At least 5 days per week for moderate-intensity PA (5–6 on a scale of 0–10 for level of physical exertion)
	At least 30 min daily of moderate intensity PA for ≥10 min each for a total of at least 150 min per week
	Exercise can include any modality that does not impose excessive orthopaedic stress, with walking being the most common type of activity
	Stationary cycling and aquatic exercise are beneficial for those with limited tolerance for weight-bearing activity
Muscle strength/endurance	At least 2 days per week
	Light intensity (40–50% of 1-repetition maximum) for subjects beginning a resistance training programme, slowly progressing to moderate intensity (60–70% of 1-repetition max). RPE = 5 to 6 (0–10 scale)
	Exercises should involve progressive weight training or weight-bearing calisthenics (either standing or seated) that include 8–10 exercises involving the 8–10 major muscle groups and at least 1 set of 10–15 repetitions per exercise or 2–4 sets of 8–25 repetitions
Flexibility	Stretch to the limits of discomfort within the ROM, to the point of mild tightness without discomfort
	>4 repetitions per muscle group
	Static: 15–60 s; PNF: hold 6 s, then a 10–30 s assisted stretch or dynamic (ballistic may be fine for individuals who participate in ballistic activities)
Other considerations	Physical activity sessions should begin with a warm-up and end with an appropriate cool-down
	Intensity and duration of exercise should be light at the beginning for deconditioned individuals or those with chronic conditions or functional limitations
	Progression of exercise should be individualised
	Initial strength training sessions using weight lifting machines should be supervised
	Obese or weight older adults may benefit to a progression of >250 min per week of moderate-intensity exercise

References

1. Eisner MD, Thompson T, Hudson LD, Luce JM, Hayden D, Schoenfeld D, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;164(2):231–6.
2. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA. 2014;311(13):1308–16.

3. Herridge MS. Recovery and long-term outcome in acute respiratory distress syndrome. Crit Care Clin. 2011;27(3):685–704.
4. Borges RC, Carvalho CR, Colombo AS, da Silva Borges MP, Soriano FG. Physical activity, muscle strength, and exercise capacity 3 months after severe sepsis and septic shock. Intensive Care Med. 2015;41(8):1433–44.
5. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20.
6. Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, et al. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Crit Care. 2015;19:196.
7. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med. 2015;4:16.
8. Gruther W, Benesch T, Zorn C, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. J Rehabil Med. 2008;40(3):185–9.
9. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
10. Segers J, Hermans G, Charususin N, Fivez T, Vanhorebeek I, Van den Berghe G, et al. Assessment of quadriceps muscle mass with ultrasound in critically ill patients: intra- and inter-observer agreement and sensitivity. Intensive Care Med. 2015;41(3):562–3.
11. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care. 2010;14(4):R127.
12. Ali NA, O'Brien JM Jr, Hoffmann SP, Phillips G, Garland A, Finley JC, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med. 2008;178(3):261–8.
13. Rehabilitation after critical illness. National Institute for Health and Clinical Excellence: Guidance. London; 2009.
14. Castro-Avila AC, Seron P, Fan E, Gaete M, Mickan S. Effect of early rehabilitation during intensive care unit stay on functional status: systematic review and meta-analysis. PLoS One. 2015;10(7):e0130722.
15. Hickmann CE, Castanares-Zapatero D, Bialais E, Dugernier J, Tordeur A, Colmant L, et al. Teamwork enables high level of early mobilization in critically ill patients. Ann Intensive Care. 2016;6(1):80.
16. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
17. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238–43.
18. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med. 2009;37(9):2499–505.
19. Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet. 2016;388(10052):1377–88.
20. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax. 2018;73(3):213–21.
21. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med. 2016;193(10):1101–10.
22. Connolly B, Denehy L. Hindsight and moving the needle forwards on rehabilitation trial design. Thorax. 2018;73(3):203–5.
23. Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. JAMA. 2018;319(1):62–75.
24. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane Collaboration systematic review. J Cachexia Sarcopenia Muscle. 2016;7(5):520–6.
25. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334–59.

26. Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med. 2007;35(1):139–45.
27. Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. Crit Care Med. 2008;36(4): 1119–24.
28. Stiller K. Safety issues that should be considered when mobilizing critically ill patients. Crit Care Clin. 2007;23(1):35–53.
29. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care. 2014;18(6):658.
30. Parry SM, Granger CL, Berney S, Jones J, Beach L, El-Ansary D, et al. Assessment of impairment and activity limitations in the critically ill: a systematic review of measurement instruments and their clinimetric properties. Intensive Care Med. 2015;41(5):744–62.
31. Major ME, Kwakman R, Kho ME, Connolly B, McWilliams D, Denehy L, et al. Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge. Crit Care. 2016;20(1):354.
32. Gosselink R, Clerckx B, Robbeets C, Vanhullenbusch T, Vanpee G, Segers J. Physiotherapy in the intensive care unit. Neth J Int Care. 2011;15:9.
33. Fink MP, Helsmoortel CM, Stein KL, Lee PC, Cohn SM. The efficacy of an oscillating bed in the prevention of lower respiratory tract infection in critically ill victims of blunt trauma. A prospective study. Chest. 1990;97(1):132–7.
34. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev. 2015;95(3):1025–109.
35. Llano-Diez M, Renaud G, Andersson M, Marrero HG, Cacciani N, Engquist H, et al. Mechanisms underlying ICU muscle wasting and effects of passive mechanical loading. Crit Care. 2012;16(5):R209.
36. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, MacMillan RR. Effect of passive stretching on the wasting of muscle in the critically ill. Nutrition. 1995;11(5):428–32.
37. Williams PE. Use of intermittent stretch in the prevention of serial sarcomere loss in immobilised muscle. Ann Rheum Dis. 1990;49(5):316–7.
38. Kwan MW, Ha KW. Splinting programme for patients with burnt hand. Hand Surg. 2002;7(2):231–41.
39. Hinderer SR, Dixon K. Physiologic and clinical monitoring of spastic hypertonia. Phys Med Rehabil Clin N Am. 2001;12(4):733–46.
40. Gibson JN, Smith K, Rennie MJ. Prevention of disuse muscle atrophy by means of electrical stimulation: maintenance of protein synthesis. Lancet. 1988;2(8614):767–70.
41. Williams N, Flynn M. A review of the efficacy of neuromuscular electrical stimulation in critically ill patients. Physiother Theory Pract. 2014;30(1):6–11.
42. Maffiuletti NA, Roig M, Karatzanos E, Nanas S. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. BMC Med. 2013;11:137.
43. Segers J, Hermans G, Bruyninckx F, Meyfroidt G, Langer D, Gosselink R. Feasibility of neuromuscular electrical stimulation in critically ill patients. J Crit Care. 2014;29(6):1082–8.
44. Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. Chest. 2003;124(1): 292–6.
45. Camargo Pires-Neto R, Fogaca Kawaguchi YM, Sayuri Hirota A, Fu C, Tanaka C, Caruso P, et al. Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects--a case series. PLoS One. 2013;8(9):e74182.
46. Thelandersson A, Nellgard B, Ricksten SE, Cider A. Effects of early bedside cycle exercise on intracranial pressure and systemic hemodynamics in critically ill patients in a neurointensive care unit. Neurocrit Care. 2016;25(3):434–9.
47. Perme C, Chandrashekar R. Early mobility and walking program for patients in intensive care units: creating a standard of care. Am J Crit Care. 2009;18(3):212–21.
48. Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. JAMA. 2008;300(14):1685–90.
49. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, et al. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. Ann Am Thorac Soc. 2017;14(5):766–77.

50. Probst VS, Troosters T, Coosemans I, Spruit MA, Pitta Fde O, Decramer M, et al. Mechanisms of improvement in exercise capacity using a rollator in patients with COPD. Chest. 2004;126(4):1102–7.
51. Chang AT, Boots R, Hodges PW, Paratz J. Standing with assistance of a tilt table in intensive care: a survey of Australian physiotherapy practice. Aust J Physiother. 2004;50(1):51–4.
52. Goldman JM, Rose LS, Williams SJ, Silver JR, Denison DM. Effect of abdominal binders on breathing in tetraplegic patients. Thorax. 1986;41(12):940–5.
53. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. Eur Respir J. 2004;23(1):34–40.
54. Chiang LL, Wang LY, Wu CP, Wu HD, Wu YT. Effects of physical training on functional status in patients with prolonged mechanical ventilation. Phys Ther. 2006;86(9):1271–81.
55. Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. Arch Phys Med Rehabil. 1998;79(7):849–54.
56. Martin UJ, Hincapie L, Nimchuk M, Gaughan J, Criner GJ. Impact of whole-body rehabilitation in patients receiving chronic mechanical ventilation. Crit Care Med. 2005;33(10):2259–65.
57. Porta R, Vitacca M, Gile LS, Clini E, Bianchi L, Zanotti E, et al. Supported arm training in patients recently weaned from mechanical ventilation. Chest. 2005;128(4):2511–20.
58. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. Eur Respir J. 2002;20(1):12–9.
59. Harrold ME, Salisbury LG, Webb SA, Allison GT. Australia, Scotland ICUPC. Early mobilisation in intensive care units in Australia and Scotland: a prospective, observational cohort study examining mobilisation practises and barriers. Crit Care. 2015;19:336.
60. Jolley SE, Moss M, Needham DM, Caldwell E, Morris PE, Miller RR, et al. Point prevalence study of mobilization practices for acute respiratory failure patients in the United States. Crit Care Med. 2017;45(2):205–15.
61. Connolly BA, Mortimore JL, Douiri A, Rose JW, Hart N, Berney SC. Low levels of physical activity during critical illness and weaning: the evidence-reality gap. J Intensive Care Med. 2017:885066617716377.
62. Koo KK, Choong K, Cook DJ, Herridge M, Newman A, Lo V, et al. Early mobilization of critically ill adults: a survey of knowledge, perceptions and practices of Canadian physicians and physiotherapists. CMAJ Open. 2016;4(3):E448–E54.
63. Dubb R, Nydahl P, Hermes C, Schwabbauer N, Toonstra A, Parker AM, et al. Barriers and strategies for early mobilization of patients in intensive care units. Ann Am Thorac Soc. 2016;13(5):724–30.
64. Hodgson CL, Capell E, Tipping CJ. Early mobilization of patients in intensive care: organization, communication and safety factors that influence translation into clinical practice. Crit Care. 2018;22(1):77.
65. Beduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, et al. Epidemiology of weaning outcome according to a new definition. The WIND study. Am J Respir Crit Care Med. 2017;195(6):772–83.
66. Penuelas O, Frutos-Vivar F, Fernandez C, Anzueto A, Epstein SK, Apezteguia C, et al. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J Respir Crit Care Med. 2011;184(4):430–7.
67. Goldstone J, Moxham J. Assisted ventilation. 4. Weaning from mechanical ventilation. Thorax. 1991;46(1):56–62.
68. Vassilakopoulos T, Zakynthinos S, Roussos C. The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med. 1998;158(2):378–85.
69. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42(5):853–61.
70. Berger D, Bloechlinger S, von Haehling S, Doehner W, Takala J, Z'Graggen WJ, et al. Dysfunction of respiratory muscles in critically ill patients on the intensive care unit. J Cachexia Sarcopenia Muscle. 2016;7(4):403–12.
71. De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med. 2007;35(9):2007–15.
72. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of diaphragm thickness during mechanical ventilation. Impact of inspiratory effort. Am J Respir Crit Care Med. 2015;192(9):1080–8.

73. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. Mayo Clin Proc. 2017;92(9):1382–400.
74. Gayan-Ramirez G, Testelmans D, Maes K, Racz GZ, Cadot P, Zador E, et al. Intermittent spontaneous breathing protects the rat diaphragm from mechanical ventilation effects. Crit Care Med. 2005;33(12):2804–9.
75. Elkins M, Dentice R. Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. J Physiother. 2015;61(3):125–34.
76. Vorona S, Sabatini U, Al-Maqbali S, Bertoni M, Dres M, Bissett B, et al. Inspiratory muscle rehabilitation in critically ill adults: a systematic review and meta-analysis. Ann Am Thorac Soc. 2018;15(6):735–44.
77. Tonella RM, Ratti L, Delazari LEB, Junior CF, Da Silva PL, Herran A, et al. Inspiratory muscle training in the intensive care unit: a new perspective. J Clin Med Res. 2017;9(11):929–34.
78. Langer D, Charususin N, Jacome C, Hoffman M, McConnell A, Decramer M, et al. Efficacy of a novel method for inspiratory muscle training in people with chronic obstructive pulmonary disease. Phys Ther. 2015;95(9):1264–73.
79. Chao PW, Shih CJ, Lee YJ, Tseng CM, Kuo SC, Shih YN, et al. Association of postdischarge rehabilitation with mortality in intensive care unit survivors of sepsis. Am J Respir Crit Care Med. 2014;190(9): 1003–11.
80. Elliott D, McKinley S, Alison J, Aitken LM, King M, Leslie GD, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. Crit Care. 2011;15(3):R142.
81. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31(10):2456–61.
82. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
83. McDowell K, O'Neill B, Blackwood B, Clarke C, Gardner E, Johnston P, et al. Effectiveness of an exercise programme on physical function in patients discharged from hospital following critical illness: a randomised controlled trial (the REVIVE trial). Thorax. 2017;72(7):594–5.
84. Pescatello LS, Arena R, Riebe D, Thompson PD. ACSM's guidelines for exercise testing & prescription. Baltimore, MD: Lippincott, Williams & Wilkins; 2014.

Nutritional Strategies

Danielle E. Bear, Lee-anne Chapple, and Zudin Puthucheary

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_20

Learning Objectives

- To understand the rationale for feeding the critically ill patient in relation to muscle wasting and functional recovery.
- To detail the steps to be undertaken for nutrition screening and assessment of critically ill patients.
- To understand how to calculate energy and protein targets.
- To be able to monitor patients receiving nutrition support.
- To assess nutritional support for those receiving non-invasive ventilation, those managing oral intake and in the post-ICU phase.

20.1 Introduction

The last decade of intensive care research and practice has seen a shift in priorities: as mortality from critical illness decreases year on year, a growing focus on survivorship has developed [1]. This has led to codification of the burden of survivorship into two distinct but overlapping syndromes: chronic critical illness [2] and post-intensive care syndrome [3]. Both of these are defined not by underpinning mechanism but by the clinical constellations of signs and symptoms – one occurs in the intensive care unit and the other following discharge. Both interact with the third newly emerging syndrome of the persistent inflammatory catabolic syndrome [4], although this relationship remains unclear.

What is becoming clearer are two underpinning aspects of physiology that cross all three syndromes – that of acute muscle wasting and inflammation. Currently, no secondary preventative strategies exist for acute muscle wasting, and to date, no rehabilitative trials have convincingly produced evidence for exercise or combined exercise and nutrition interventions [5]. At this point in time, the best strategy for prevention of both chronic critical illness and the physical aspects of post-intensive care syndrome remains that of minimising muscle wasting. This is nutritionally challenging, and the few trials of increasing nutrition delivery addressing muscle wasting and/or functional outcomes have yet to show good evidence for this as an intervention [6–10]. It may be that simple additional nutritional delivery may not be enough in the setting of inflammation; however, this chapter will outline current strategies and considerations that are considered best practice in this area.

20.2 Physiology of Muscle Wasting

In health, muscle mass is maintained by a balance of muscle protein synthesis and muscle protein breakdown, known as muscle protein homeostasis [11]. The drivers of this balance are relatively well known [12]. In humans (unlike rodents), muscle protein synthesis is facilitative, that is, a process that responds both to stimulatory (e.g. amino acids) and suppressive (e.g. starvation, immobilisation, and inflammatory) stimuli. Conversely, muscle protein breakdown is adaptive in nature. Exercise is a more complex stimulus. Resistance exercise alone is catabolic in nature [13], though the ingestion of amino acids then results in rebound anabolism [14]. Insulin does not stimulate muscle protein synthesis but can suppress muscle protein breakdown [15]. Alone, insulin treatment results in upregulation of anabolic signalling. Subsequent amino acid ingestion results in a synergistic effect on increasing muscle protein synthesis [16].

Muscle protein homeostasis in critical illness is not as straightforward, and the dominant process responsible for loss of muscle mass likely varies with time. In acute critical illness, muscle protein synthesis is suppressed and not responsive to nutrition delivery [17]. Over the period of critical illness, there is a steady variable recovery of synthetic function. Muscle protein breakdown is, however, elevated relative to muscle protein synthesis at all stages, even during chronic critical illness, leading to a net catabolic state [18].

The process of protein synthesis is highly energy dependent [19] – thus, while caloric intake is not directly linked to synthetic function, it would seem likely that a lack of cellular energy (defined by Adenosine TriPhosphate content) would lead to anabolic suppression.

An often under-discussed aspect of muscle protein homeostasis in the critically ill is the effect of age. Elderly subjects have the same basal muscle protein synthesis and breakdown rates as younger subjects [20]. However, protein ingestion to stimulate muscle protein synthesis requires relatively higher protein intakes in the elderly relative to younger subjects [21]. This phenomena has been termed anabolic resistance. Elderly subjects also do not have the same blunting of muscle protein breakdown seen in response to insulin in younger subjects [22], and therefore this group of critically ill patients may respond differently to a given treatment. However, at present, the most appropriate nutrition intervention for this group is unknown.

20.3 Rationale for Nutrition Interventions

Although there is little evidence for the role of increased nutrition delivery in reducing muscle wasting and improving the recovery of critically ill survivors, the biological rationale is sound [23]. Along with this goal, provision of early enteral nutrition is thought to reduce oxidative stress, modulate the immune response, and lead to improvements in gut integrity, thereby reducing the risk of bacterial translocation and subsequent infection [24]. For these reasons, providing nutrition support during critical illness is considered a necessary therapy rather than a supportive treatment. In addition, the current hypothesis suggests that nutrition in the post-ICU phase is equally as important as during the acute phase and that attention should be paid to appropriate nutrition support across the continuum of care [23].

20.4 Nutrition Assessment

A thorough nutrition assessment should include the following in this order:

- Nutrition screening to determine nutrition risk
- Assessment of nutritional status
- Calculation of energy and protein targets

20.4.1 Nutrition Risk

While a large number of patients are admitted to intensive care, many will stay for short periods only. Therefore, it is important to be able to identify those patients for which nutrition therapy will be of greatest benefit. In the acute care setting, the use of a validated

screening tool has been associated with improved nutrition care and reduced rates of malnutrition [25]. A wide array of nutrition risk screening tools are available. Those commonly used in ICU include the Malnutrition Universal Screening Tool (MUST), the Nutrition Risk Screening-2002 tool, and the Nutrition Risk in the Critically Ill (NUTRIC) score. The MUST relies on the ability to obtain a BMI and reported weight loss. In this population, self-reported weight loss is challenging to obtain, and weight measures are influenced by oedema as a result of fluid resuscitation. The European Society of Parenteral and Enteral Nutrition recommends the use of NRS-2002 in the acute care setting [26]. However, this tool provides a 'severe' score for all intensive care patients with an APACHE >10 and relies on reported weight loss/dietary intake and, hence, provides little guidance as to which patients are at greatest nutritional risk in this population. Therefore, the applicability of these to the critically ill population is limited. Given these difficulties, Heyland and colleagues developed the Nutrition Risk in the Critically Ill (NUTRIC) score [27], which has been shown to predict mortality and length of ICU stay and mechanical ventilation [28, 29]. However, this tool also suffers from limitations including the time-consuming nature of calculating two of the variables (SOFA and APACHE II) and the lack of any direct measures of nutritional status. Additionally, available tools neglect to consider those patients for whom their specific injury and the intensive care stay alone will influence nutrition status, such as trauma patients who were pre-morbidly well-nourished, those with a long ICU stay, and those who had a long hospital admission prior to entering the ICU where cumulative nutritional deficits are likely. Hence, nutrition risk screening should also contemplate the *future* likelihood of nutritional deficits. Regardless of the chosen tool, it is recommended that nutrition risk screening takes place within 48 h of ICU admission [30] and that the additional factors mentioned above are given consideration when determining the overall nutrition risk of a patient.

20.4.2 Assessment of Nutritional Status

For patients at high nutrition risk, a nutrition assessment should be conducted by a qualified healthcare professional, preferably a dietitian, to provide a clinical diagnosis of the patients' nutritional status and corresponding treatment plan [30]. In addition, all patients in ICU for >7 days or those requiring artificial nutrition support should have a nutrition assessment conducted. A number of nutrition assessment tools are recommended for use in the acute care setting including Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and Patient-Generated Subjective Global Assessment. The European Society of Parenteral and Enteral Nutrition has also recently developed a consensus statement on the diagnostic criteria for malnutrition, which categorises based on weight loss, body mass index (BMI), or fat-free mass index [31]. However, these tools rely on patient reports of recent weight loss and dietary intake which is challenging to collect in a sedated and mechanically ventilated population. A good nutritional assessment should not be limited to just nutritional intake but should consider the whole clinical picture, including biochemical, clinical (Fig. 20.1), and anthropometry measures as described below.

20.4.2.1 Anthropometry

Weight is most frequently used as a measure of nutrition status in dietetic critical care practice [32], yet is influenced by fluid shifts and, therefore, may not be appropriately reflective of body composition in ICU patients. In addition, patients may be overweight,

Variable	Assessment	Monitoring
Anthropometry	• Weight, BMI and limb circumference should be interpreted with caution • Muscle ultrasound, CT and BIA are currently research tools only	• Changes in anthropometrical indices such as muscle size or mass
Biochemistry	• There are no reliable biochemical markers in this setting to date • Albumin and pre-albumin are unreliable in this setting	• Fluctuations in blood glucose • Electrolytes • Liver and renal function • Inflammatory markers (eg. CRP)
Clinical	• Poor tolerance to feeding • Extended periods of fasting • Projected length of ICU stay	• Feeding tolerance and potential interruptions • Medical status and trajectory of recovery • Medication review (eg. sedatives, diuretics and prokinetcs)
Nutritional	• Previous nutritional intake (although may be difficult to obtain)	• Cumulative energy and protein deficits (aiming >80% prescribed amounts) • Non-nutritive energy (eg. propofol, intravenous glucose, citrate)

Fig. 20.1 Nutrition assessment and monitoring criteria. *BMI* Body Mass Index, *CT* Computed Tomography, *BIA* Bioelectrical Impedance Analysis, *CRP* C-reactive protein, *ICU* Intensive Care Unit

yet have significant sarcopenia that is not identified by traditional anthropometric measures. A common assessment that can be conducted in ICU is the medical component of the SGA tool [33], a visual assessment of muscle wasting which has been shown to predict outcomes in ICU patients [34, 35].

In recent years, there has been a push to develop more objective measures of muscle mass that can be used in the intensive care setting. The use of ultrasonography to measure muscle size has been shown to be reproducible by clinicians without prior ultrasound expertise [36], is representative of total lean body mass [37], and is associated with poorer self-reported functional status 3 months after ICU discharge [37]. The extent to which nutrition can influence ultrasound-derived muscle size needs to be ascertained before this can be implemented as a clinical tool. Furthermore, bioelectrical impedance, in which a small electrical current passed through the body, provides an estimate of fat mass, fat-free mass, and intra- and extracellular fluid [38]. While some studies have shown that fluid shifts influencing body weight impede the implementation of bio-impedance in assessing nutritional status [39], the potential use of phase angle – a raw parameter derived from this technique which is not influenced by hydration levels – is currently being explored [40]. There is also interest in the use of computed tomography scans of the 3rd lumbar region to estimate muscularity which has been shown to predict ICU- and ventilator-free days and mortality [41]. However, this technique remains a research tool at present due to the expertise required, time-intensive nature of measurement, and radiation dose restricting use to those conducted when clinically indicated only.

Practice Points

- Nutrition risk screening should be conducted for all ICU patients within 48 h of admission (Fig. 20.2)
- A holistic assessment of nutrition status should occur for all patients deemed at nutritional risk or expected to have a prolonged ICU stay (Fig. 20.1).
- Measures of nutrition status should be interpreted with caution, considering the medical status of the patient, and, where possible, include an objective measure of muscle mass
- As a patients' clinical condition can change rapidly in the ICU, nutrition assessment should be undertaken at least weekly or when clinical condition notably changes (Figs. 20.1 and 20.2)

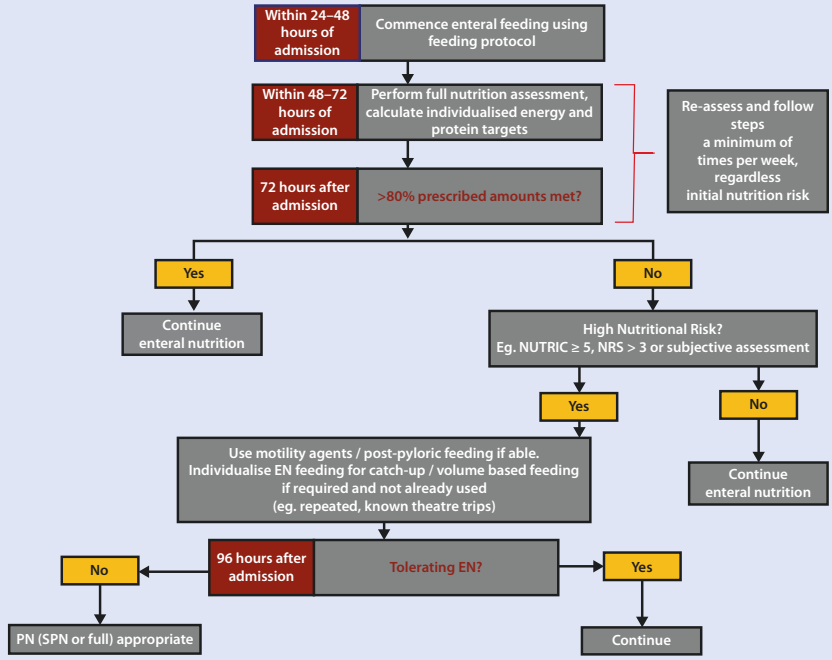


Fig. 20.2 Decision-making tool for feeding during critical illness. *EN* Enteral Nutrition, *PN* Parenteral Nutrition, *SPN* Supplemental Parenteral Nutrition, *NUTRIC* NUTrition RIsk in the Critically Ill, *NRS* Nutrition Risk Screening

20.5 Calculating Energy and Protein Targets

Optimal energy and protein requirements for critically ill patients are not yet known. Although guidelines recommend adjusting energy targets according to the phase of critical illness [24, 42], there is currently no consensus definition on how to determine a shift from one phase to another. However, it is clear that targets for energy and protein should be individualised and revised over the course of critical illness, including when the clinical condition changes and once the patient is discharged to the ward (Fig. 20.2).

20.5.1 Energy

Currently, hypocaloric feeding over the first week of ICU admission is advocated [24]. The basis for this is to reduce the risk of overfeeding as the endogenous production of glucose cannot be measured at the bedside and thus cannot be accounted for in feeding regimens [43]. Studies investigating the effect of hypocaloric or trophic vs. full enteral feeding over the first week of ICU have not shown benefit or harm in terms of mortality and length of stay [44, 45]. The effect on muscle wasting and long-term recovery is not known, although the use of an early goal-directed nutrition strategy did not improve quality of life at 6-month post-discharge from the ICU [46]. However, methodological limitations need to be considered when interpreting these studies, particularly the short the duration of the nutrition intervention which is unlikely to lead to a long-term benefit [23].

The currently accepted definition for hypocaloric feeding is 70% of measured energy expenditure [47] or 80% using a predictive equation [48]. Again, this is in relation to a reduction in mortality only.

Whichever strategy is chosen (hypocaloric or full feeding), the gold standard for determining energy targets is indirect calorimetry [24]. Traditionally, cost and labour limitations have prevented its widespread use. However, a model developed specifically for mechanically ventilated patients has recently been made available and may help to overcome the cost barrier. Nonetheless, not all patients are eligible for the use of indirect calorimetry (e.g. FiO2 > 60%, CRRT, air leaks in ventilation circuit, including chest drains), and in its absence predictive equations should be used (Table 20.1).

Table 20.1 Common prediction equations for use in critical care

Harris-Benedict	Males: (13.7516 × *W*) + (5.003 × *H*) − (6.755 × *A*)
	Females: 655.0955 + (9.5634 × *W*) + (1.8496 × *H*) − (4.6756 × *A*)
Ireton-Jones (1992)	(5 × *W*) − (10 × *A*) + (281 × sex) + (292 × trauma) + (851 × burn) + 1925
Ireton-Jones (1997)	(5 × *W*) − (11 × *A*) + (244 × sex) + (239 × trauma) + (840 × burn) + 1784.
Penn State (1998)	(Harris-Benedict × 1.1) + (*T*max × 140) + (VE × 32) − 5340
	Uses actual body weight in non-obese and adjusted bodyweight (25%) in obese
Penn State (2003)	(Harris-Benedict × 0.85) + (*T*max × 175) + (VE × 33) − 6344
Penn State (m)	(Mifflin-St Jeor × 0.96) + (*T*max × 167) + (Ve × 31) − 6212
ACCP	25 kcal × kg
Mifflin-St Jeor	Males: (10 × *W*) + (6.25 × *H*) − (5 × *A*) + 5
	Females: (10 × *W*) + (6.25 × *H*) − (5 × *A*) − 161

W = Weight in kg; *H* = Height in cm; *A* = Age in years; For sex, 1 is male, 0 is female; trauma present = 1 no trauma = 0; burns present =, 1, no burns = 0; Tmax = maximum body temperature last 24 h; VE = minute ventilation in L/min at time of measurement; Kcal = calorie

Several predictive equations exist for estimating energy targets in critically ill patients (Table 20.1); however, the most frequently used and cited is the weight-based equation, 25 kcal/kg. Several issues exist with weight-based equations including which weight to use when patients fall outside of the normal range for body mass index, and subsequent lack of attention afforded to recalculation of energy targets when the clinical condition changes due to the static nature of this equation. When using predictive equations, it is important to consider the specific variables with which the equation was validated and use these for the best accuracy. This includes checking whether actual, ideal, or adjusted weight was used and the patient population in which the equation was derived (e.g. trauma).

Little is known about the energy requirements of patients who are undergoing different levels of rehabilitation, on non-invasive ventilation (NIV) or not ventilated in the ICU or in the recovery phase post-ICU. For this reason, close monitoring of potential complications from underfeeding and overfeeding energy should occur.

Practice Point

There is a tendency when using weight-based equations to continue on this for the duration of the patient's ICU admission due to the lack of an updated weight. If using a weight-based equation, close attention must be paid to changes in the patient's clinical condition which may affect energy expenditure (e.g. pyrexia, agitation, rehabilitation), and clinical judgement should be used accordingly.

20.5.2 Protein

Recently, recommendations for protein intake in the critically ill have been revised to include higher targets [24]. It would seem reasonable that this strategy would reduce the loss of muscle associated with critical illness and indeed improve recovery of muscle mass in the post-ICU phase; however, robust evidence to support this is lacking. Nonetheless, higher protein intakes have been associated with reduced mortality in observational studies, and a minimum of 1.2 g/kg/day is recommended with adjustments for different clinical situations being appropriate. Table 20.2 shows protein recommendations for different clinical conditions.

Table 20.2 Protein recommendations for different clinical conditions in the critically ill

Patient group	Protein target
General ICU	1.2–1.5 g/kg
Continuous renal replacement therapy	1.5–1.7 g/kg
Burns	1.5–2.0 g/kg
Trauma	1.3–1.5 g/kg
Obese	2.0–2.5 g/kg (ideal body weight)

Practice Point
An ideal body weight should be used for patients who are considered obese according to BMI cut-offs. Actual body weight can be used for those patients with a normal BMI and those who are underweight. There is no consensus on how to derive ideal body weight, but a consistent approach to this is warranted in clinical practice.

20.6 Enteral and Parenteral Nutrition

20.6.1 Early Enteral Nutrition and Feeding Protocols

Although not necessarily related to muscle mass and recovery, commencing early enteral nutrition in patients not expected to manage sufficient oral intake within 48 h (e.g. those who are mechanically ventilated either invasively or non-invasively) is recommended [24] (Fig. 20.2). The easiest way to achieve this is to use a feeding protocol. The use of feeding protocols in this patient population is associated with a shorter time to feeding as well as time to meeting nutritional targets (energy and protein) [24].

Although each ICU will have a unique feeding protocol to suit their patient case mix, common features should include the following:

- Nurse-led and out of hours use of enteral nutrition
- Guidance for managing feeding intolerance (e.g. prokinetics, post-pyloric feeding tubes, parenteral nutrition)
- Guidance for the management of patients at risk of refeeding syndrome
- Referral criteria for specialist nutrition assessment

Providing enteral nutrition alone has been shown to lead to under delivery of nutrition. This is as a result of frequent interruptions in feeding due to procedures and gastrointestinal intolerance. Given the importance of meeting energy and protein targets, daily monitoring of nutrition delivery (preferably via an electronic medical notes system) is imperative to enable timely correction of any deficits incurred (Figs. 20.1 and 20.2). Strategies to increase the delivery of nutrition include the following:

- Volume-based feeding
- Having available a guideline for when to stop and start enteral feeding for procedures
- Post-pyloric feeding
- Protein supplements
- Supplemental parenteral nutrition

Practice Point

- Currently available enteral formula may not be able to meet full energy and protein targets.
- Using a concentrated feed (1.5 kcal/ml) has been shown to meet energy targets over a 1 kcal/ml formula.
- As commercial formula is often low in protein, a protein supplement may be required.

20.6.2 Use of Total Parenteral Nutrition and Supplemental Parenteral Nutrition

The use of parenteral nutrition (PN) in critically ill patients is controversial [43]. However, it is important to understand the differences between total parenteral nutrition (TPN) and supplemental parenteral nutrition (SPN). TPN is defined as providing all nutrition targets via the parenteral route. Trophic feeding may be used in some instances for gut integrity, but it is not expected that this will contribute to the overall energy and protein intake. On the other hand, SPN is used as a supplement to enteral nutrition when 60% or less of energy and/or protein targets are being met.

When provided at the same dose, EN and PN derive the same outcome in terms of mortality, length of stay, and infectious complications [49, 50]. However, this appears to be related to TPN only and not SPN. Current guidelines suggest withholding PN for 7 days in patients not considered to be at high nutritional risk [24]. However, with the lack of a robust nutrition risk score, the reality of clinical practice may be different. In this instance, consideration should be given to the risk/benefit of providing PN, including the expected duration of PN as short-term PN in any form is unlikely to be beneficial.

Studies investigating the effect of PN on muscle wasting and recovery are limited. One study has shown that providing at least 1.2 g/k/day amino acids in the form of parenteral nutrition improved grip strength, muscle wasting, and fatigue (secondary outcomes) compared with 0.8 g/kg/day [7]. However, this benefit has not been seen consistently with a study of early vs late SPN indicating slower recovery using the MRC-sum score [8] and no difference on muscle wasting in the patients receiving early SPN [10]. Given the conflicting data, care must be taken to consider the nutrition status of the patient and potential that PN will lead to benefit.

Practice Points

- Care must be taken not to overfeed energy when providing parenteral nutrition in any form.
- Overfeeding may be more common when SPN is used, and therefore frequent monitoring and adjustment of both EN and PN is required.

20.7 Monitoring of Nutrition Support

Given the controversy of the optimal nutrition prescription, it is important to ensure the appropriate monitoring of nutrition status and intake (Figs. 20.1 and 20.2). Regular monitoring of nutrition progress allows for prompt reassessment and adaption of nutrition care plans. Similar to the assessment of nutrition status, monitoring should incorporate measures of anthropometry, biochemistry, clinical indicators, and nutritional intake. Consideration of longer-term outcomes including functional status and quality of life is also required. For enterally and parenterally fed patients, a complete assessment of their clinical status, biochemical indicators, and nutrition intake should occur ideally daily, but at least three times per week. Changes in anthropometry should be assessed weekly for all patients, regardless of feeding route, and can incorporate those measures detailed in the assessment section above. Factors to monitor are reported in Fig. 20.2.

20.8 Additional Considerations

20.8.1 Oral Intake

While critical illness is usually associated with mechanically ventilated patients receiving artificial nutrition support, there are also a substantial number of patients that will enter the ICU for whom nutrition needs will be obtained orally [51]. Orally fed patients feature little in the critical care nutrition literature, and hence there are no guidelines that provide recommendations on how to optimise oral nutrition therapy in critical illness.

Oral intake may be reduced in critical illness due to a number of clinical factors. Patients often experience dysphagia as a consequence of injury or dysfunction following orotracheal intubation due to localised swelling or laryngeal tissue damage [52]. In an observational study of traumatic brain-injured patients admitted to ICU, 85% of patients required a modified texture diet during their hospital admission [53], and dysphagia has been shown to remain in one third of ICU survivors at hospital discharge [54, 55]. Fatigue can also affect oral intake by reducing chewing ability with patients reporting fatigue in 75% of patients during their ICU stay [56], at meals 2 weeks after hospital discharge [57], and remains in 37% 12 months after ICU admission [58]. In addition, a reduced appetite has been associated with decreased oral intake in hospitalised patients [57].

In the intensive care setting, there are two subsets of patients for whom nutritional adequacy from oral intake should receive more attention.

20.8.1.1 Non-invasive Ventilation

For patients who receive non-invasive ventilation, oral intake can be disrupted. Reeves et al. reported nutritional deficits during non-invasive ventilation (NIV) are substantially below those prescribed with 75% of patients consuming <80% of goal calorie and protein prescription [59], and Terzi and colleagues conducted a retrospective study that showed more than half of patients receive no nutrition in the first 2 days of NIV [60]. Despite many of these patients having a shorter ICU length of stay than ventilated patients, the potential for cumulative nutritional deficits following ICU discharge means nutritional intake of these patients should be assessed.

20.8.2 Post-extubation

Secondly, following removal of the endotracheal tube, simultaneous removal of the enteral feeding tube may occur. Few studies have explored nutritional intake in patient's post-extubation. Using a modified 24-h multiple pass questionnaire, Peterson and colleagues assessed oral intake in 50 patients for 7 days following extubation and reported mean energy and protein intakes failed to meet more than 50% of prescriptions on any day [61]. Similarly, Moisey et al. measured nutritional intake using weighed food records for 7 consecutive days following liberation from mechanical ventilation and reported energy and protein adequacy from oral nutrition to be 75% and 30%, respectively [62].

20.8.3 Post-ICU Nutrition

While it is known that patients experience significant nutritional deficits during their intensive care admission, discharge to the post-ICU acute ward does not signal the end of their medical journey. Patients may spend just a short time of their hospital stay in the ICU, and hence post-ICU nutrition becomes central to recovery. However, until recently there has been very little attention paid to nutritional intake during the acute hospital period. In a subset of ICU patients admitted with a traumatic brain injury, Chapple et al. quantified energy and protein deficits not only during the ICU admission but also on the post-ICU acute ward [53].

It is likely that the reason for poor nutritional rehabilitation on the post-ICU ward is multifactorial. Interviews with medical and nursing staff caring for head-injured patients across the continuum of the hospital stay reported that nutritional management decreases after ICU discharge, in terms of priority, perceived importance, and frequency [63]. Further, Merriweather and colleagues [64] conducted semi-structured interviews with 17 patients following ICU discharge and reported a number of organisational issues were responsible for reduced nutritional care after ICU discharge, including disjointed discharge planning and inflexible meal service [64]. Other aspects of transitional care have also been documented such as poor communication during hand-over processes [65, 66]. Therefore, greater focus should therefore be placed on nutritional intake over the entire hospital stay.

Practice Points

- Strategies to increase oral intake need to consider factors that affect intake.
- Nutritional intake should be considered as cumulative deficits not just during the ICU admission but across the entire hospital stay.
- A clear nutritional treatment plan, which includes an overview of nutritional intake and status during ICU, should be communicated to all health professionals on ICU discharge.

Take Home Messages

- Nutrition support during critical illness is considered a necessary therapy.
- Appropriate nutrition support should be provided across the continuum of care, including in the acute phase of critical illness, on the ward, and extending to rehabilitation and into the community as required.
- A thorough nutritional assessment should be undertaken within 72 h of admission to the ICU and should be repeated frequently throughout the ICU and hospital stay.
- Feeding protocols can help to commence early enteral feeding and manage the cumulative nutrition deficits that arise over the course of ICU admission.
- Nutrition support includes the consideration of oral intake and should not stop when the patient is extubated or on NIV.
- Nutrition in the post-ICU phase has the potential to impact on recovery.

References

1. Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. Ann Intern Med. 2010;153(3):204–5.
2. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182(4):446–54.
3. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9.
4. Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45(2):253–62.
5. Hodgson C, Cuthbertson BH. Improving outcomes after critical illness: harder than we thought! Intensive Care Med. 2016;42(11):1772–4.
6. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188(5):567–76.
7. Ferrie S, Allman-Farinelli M, Daley M, Smith K. Protein requirements in the critically ill: a randomized controlled trial using parenteral nutrition. JPEN J Parenter Enteral Nutr. 2016;40(6):795–805.
8. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621–9.
9. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130–8.
10. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Guiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013;41(10):2298–309.
11. Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. J Appl Physiol. 2009;107(3):645–54.
12. Rennie MJ. Muscle protein turnover and the wasting due to injury and disease. Br Med Bull. 1985;41(3):257–64.
13. Pitkanen HT, Nykanen T, Knuutinen J, Lahti K, Keinanen O, Alen M, et al. Free amino acid pool and muscle protein balance after resistance exercise. Med Sci Sports Exerc. 2003;35(5):784–92.
14. Moore DR, Tang JE, Burd NA, Rerecich T, Tarnopolsky MA, Phillips SM. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. J Physiol. 2009;587(Pt 4):897–904.
15. Trommelen J, Groen BB, Hamer HM, de Groot LC, van Loon LJ. Mechanisms in endocrinology: Exogenous insulin does not increase muscle protein synthesis rate when administered systemically: a systematic review. Eur J Endocrinol. 2015;173(1):R25–34.
16. Greenhaff PL, Karagounis LG, Peirce N, Simpson EJ, Hazell M, Layfield R, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. Am J Physiol Endocrinol Metab. 2008;295(3):E595–604.
17. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
18. Gamrin-Gripenberg L, Sundstrom-Rehal M, Olsson D, Grip J, Wernerman J, Rooyackers O. An attenuated rate of leg muscle protein depletion and leg free amino acid efflux over time is seen in ICU long-stayers. Crit Care. 2018;22(1):13.
19. Kafri M, Metzl-Raz E, Jona G, Barkai N. The cost of protein production. Cell Rep. 2016;14(1):22–31.
20. Markofski MM, Dickinson JM, Drummond MJ, Fry CS, Fujita S, Gundermann DM, et al. Effect of age on basal muscle protein synthesis and mTORC1 signaling in a large cohort of young and older men and women. Exp Gerontol. 2015;65:1–7.
21. Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol. 2009;587(1):211–7.

22. Wilkes EA, Selby AL, Atherton PJ, Patel R, Rankin D, Smith K, et al. Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. Am J Clin Nutr. 2009;90(5):1343–50.
23. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017;21(1):226.
24. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159–211.
25. Eglseer D, Halfens RJG, Lohrmann C. Is the presence of a validated malnutrition screening tool associated with better nutritional care in hospitalized patients? Nutrition. 2017;37:104–11.
26. Kondrup J. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22(4):415–21.
27. Heyland D, Dhaliwal R, Jiang X, Day A. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15:R268.
28. Kalaiselvan MS, Renuka MK, Arunkumar AS. Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: a prospective observational study. Indian J Crit Care Med. 2017;21(5):253–6.
29. de Vries MC, Koekkoek WK, Opdam MH, van Blokland D, van Zanten AR. Nutritional assessment of critically ill patients: validation of the modified NUTRIC score. Eur J Clin Nutr. 2018;72(3):428–35.
30. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49–64.
31. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition – an ESPEN consensus statement. Clin Nutr. 2015;34(3):335–40.
32. Ferrie S, Tsang E. Monitoring nutrition in critical illness: what can we use? Nutr Clin Pract. 2017:884533617706312.
33. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? J Parenter Enter Nutr. 1987;11(1):8–13.
34. Bector S, Vagianos K, Suh M, Duerksen DR. Does the subjective global assessment predict outcome in critically ill medical patients? J Intensive Care Med. 2016;31(7):485–9.
35. Sungurtekin H, Sungurtekin U, Oner O, Okke D. Nutrition assessment in critically ill patients. Nutr Clin Pract. 2008;23(6):635–41.
36. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN J Parenter Enteral Nutr. 2014;38(7):886–90.
37. Chapple L, Deane AM, Williams LT, Strickland R, Schultz C, Lange K, et al. Longitudinal changes in anthropometry and impact on self-reported physical function following traumatic brain injury. Crit Care Resusc. 2017;19(1):29–36.
38. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. JPEN J Parenter Enteral Nutr. 2015;39(7):787–822.
39. Baldwin CE, Paratz JD, Bersten AD. Body composition analysis in critically ill survivors: a comparison of bioelectrical impedance spectroscopy devices. JPEN J Parenter Enteral Nutr. 2012;36(3):306–15.
40. Kuchnia A, Earthman C, Teigen L, Cole A, Mourtzakis M, Paris M, et al. Evaluation of bioelectrical impedance analysis in critically ill patients: results of a multicenter prospective study. JPEN J Parenter Enteral Nutr. 2017;41(7):1131–8.
41. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17(5):R206.
42. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25(2):210–23.
43. Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015;19:35.
44. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med. 2015;372(25):2398–408.
45. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Rice TW, Wheeler AP, Thompson BT, Steingrub J, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795–803.

46. Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017;43(11):1637–47.
47. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016;20(1):367.
48. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! Crit Care Med. 2011;39(12):2619–26.
49. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673–84.
50. Reignier J, Boisrame-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133–43.
51. Bendavid I, Singer P, Theilla M, Themessl-Huber M, Sulz I, Mouhieddine M, et al. Nutrition day ICU: a 7 year worldwide prevalence study of nutrition practice in intensive care. Clin Nutr. 2017;36(4):1122–9.
52. Macht M, White SD, Moss M. Swallowing dysfunction after critical illness. Chest. 2014;146(6):1681–9.
53. Chapple LS, Deane AM, Heyland DK, Lange K, Kranz AJ, Williams LT, et al. Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury. Clin Nutr. 2016;35(6):1315–22.
54. Kruser JM, Prescott HC. Dysphagia after acute respiratory distress syndrome. Another lasting legacy of critical illness. Ann Am Thorac Soc. 2017;14(3):307–8.
55. Schefold JC, Berger D, Zürcher P, Lensch M, Perren A, Jakob SM, et al. Dysphagia in mechanically ventilated ICU patients (DYnAMICS). Crit Care Med. 2017;45(12):2061–9.
56. Cajanding RJ. Causes, assessment and management of fatigue in critically ill patients. Br J Nurs. 2017;26(21):1176–81.
57. Sorensen J, Holm L, Frost MB, Kondrup J. Food for patients at nutritional risk: a model of food sensory quality to promote intake. Clin Nutr. 2012;31(5):637–46.
58. Steenbergen S, Rijkenberg S, Adonis T, Kroeze G, van Stijn I, Endeman H. Long-term treated intensive care patients outcomes: the one-year mortality rate, quality of life, health care use and long-term complications as reported by general practitioners. BMC Anesthesiol. 2015;15:142.
59. Reeves A, White H, Sosnowski K, Tran K, Jones M, Palmer M. Energy and protein intakes of hospitalised patients with acute respiratory failure receiving non-invasive ventilation. Clin Nutr. 2014;33(6):1068–73.
60. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. Crit Care. 2017;21(1):293.
61. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. J Am Diet Assoc. 2010;110:427–33.
62. Moisey L. A comprehensive assessment of nutritional status and factors impacting nutrition recovery in hospitalized, critically ill patients following liberation from mechanical ventilation. Waterloo: University of Waterloo; 2017.
63. Chapple LS, Chapman M, Shalit N, Udy A, Deane A, Williams L. Barriers to nutrition intervention for patients with a traumatic brain injury: views and attitudes of medical and nursing practitioners in the acute care setting. JPEN J Parenter Enteral Nutr. 2017;148607116687498
64. Merriweather J, Smith P, Walsh T. Nutritional rehabilitation after ICU – does it happen: a qualitative interview and observational study. J Clin Nurs. 2014;23(5–6):654–62.
65. Chaboyer W, James H, Kendall M. Transitional care after the intensive care unit: current trends and future directions. Crit Care Nurse. 2005;25(3):16–8, 20-2, 4-6 passim; quiz 9
66. Häggström M, Asplund K, Kristiansen L. Struggle with a gap between intensive care units and general wards. Int J Qual Stud Health Well Being. 2009;4(3):181–92.

Nutritional Rehabilitation in the ICU

Pablo Lucas Massanet, Thomas Lescot, and Jean-Charles Preiser

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_21

21

Learning Objectives

At the end of this chapter, you should have learned much more about:

- *Food intake physiology and critical illness disorders*
- *Possible strategies to improve food intake in the ICU and organisational aspects*
- *Priorities for future research*

21.1 Introduction

Patients that survive intensive care will have to pay back that organic debt. As a result of their prolonged catabolic state, critically ill patients suffer severe undernutrition, which is characterised by muscle-mass meltdown, insulin resistance, vitamin deficiency, impaired healing, bedsores, immobility, cognitive impairment in some cases and susceptibility to infections and depression [1]. The loss of muscle proteins is a major consequence of critical illness, and the rebuilding of muscle will require huge intakes of calories and proteins. Unfortunately, adequate nutritional intakes, after the acute phase of critical illness, are frequently limited by several different factors. Although data on nutritional rehabilitation during the recovery phase of critical illness are rare, similar concerns have been managed by specialists of several other fields. Inappropriately low nutritional intakes can be related to psychological disorders, alterations in taste, swallowing disorders as well as patients missing their meal due to organization procedures. Nutritional recommendations in this field are scarce and not necessarily applied [2].

Specifically, the following issues will be developed:

1. *Food intake physiology and critical illness disorders*
2. *Possible strategies to improve food intake in the ICU and organisational aspects*
3. *Priorities for future research*

21.1.1 Food Intake Physiology and Critical Illness Disorders

From a practical viewpoint, three phases can be distinguished, even if they share some common regulatory mechanisms: a pre-prandial phase, a prandial phase and a post-prandial phase. In the critically ill, the pre-prandial phase is altered by a loss of appetite, the prandial phase can be altered by the presence of swallowing disorders and the post-prandial phase can be characterised by impairment of gastric emptying, gut motility and alterations in the feeling of satiety.

21.1.1.1 Pre-prandial Phase

Physiological Regulation

This phase is sometimes called the "cephalic phase". After stimulation, multiple responses are set off including salivation, gastric secretion and hormonal secretion. Hunger (as measured by visual analogue scales) increases on sight of pleasant food [3]. The gastrointestinal tract releases a peptide called ghrelin that acts as a stimulator of appetite [4]. Its plasma levels increase before food intake and decrease progressively in the post-prandial period. This would suggest that ghrelin probably has an important role in initiating food intake, triggered by hypothalamus [5]. Conversely, peptide YY (PYY) is secreted by colon and rectum and, to a lesser extent, by pancreas, small-intestine and stomach. PYY seems to modulate gastrointestinal motility: pharmacological doses of PYY slow gastric emptying and small-intestine transit.

Loss of Appetite During Critical Illness

Psychological Factors

A review from Cutler et al. [6] has described different patient experiences in ICUs. Often, patients cannot make the distinction between reality and hallucination. This is probably due to psychological changes associated with the drugs used in critically ill patients. At the same time, they describe near-death experiences due to hospitalisation in ICU. This is a major obstacle for patients in finding a new meaning to their life and realising that they are indeed alive. Gradually, the patients recognise the transformation of their body, as well as the effect of the disease itself. At the same time, patients begin to understand their resuscitation story (defined as "nightmare" by some patients), thanks to the information given by the medical staff. Family environment is important for support and love, but it reminds patients of life outside the ICU. These feelings throughout hospitalisation in ICU can cause depressive episodes, major anxiety, insomnia and even panic attacks [6]. Jubran and colleagues have shown in a prospective study of 336 critically ill patients during weaning phase that 42% of the patients were diagnosed with depression. In this same group, respiratory distress and mortality during the weaning phase were significant [7]. All these symptoms (depression, anxiety, low mood, pain, sleep disturbances, etc.) may affect palatability of food, contribute to the anorexia of critically ill patients and negatively impact food intake.

Sensory Function in ICU

Sensory stimulation and vision is an active part of food intake involved in the "cephalic phase". Various diseases (cirrhosis, Guillain-Barré syndrome, COPD, oncological disease, kidney failure, etc.) [8, 9] can produce taste alterations (hypogeusia, dysgeusia) and a smell perturbation (hyposmia, anosmia). On the other hand, many drugs are implicated in the loss or distortion of meaning (chemotherapy, antibiotics, anti-inflammatory, anti-hypertensive, etc.) [10, 11]. These changes may also decrease palatability of food, affecting food intake, and thus generate anorexia and malnutrition [12]. An interesting study of nutritional care and patients' experiences in ICU reported taste changes during the first few days post transfer to the ward. Some patients reported that food is salty, and others experienced a metallicky taste when eating [13].

Changes in Gut-Derived Hormones

Nematy and colleagues conducted a prospective observational study on blood levels of ghrelin and peptide YY in ICU patients and healthy volunteers (control group). Sixty patients were included in the study, and the levels of ghrelin and PYY were analysed on days 1, 3, 5, 14, 21 and 28. Critically ill patients showed lower plasma concentrations of ghrelin as compared to healthy volunteers (control group). In contrast, PYY levels were higher in ICU patients compared to healthy volunteers. Ghrelin levels increased during hospitalisation and were still high on day 28. A positive relation was found between hunger in the fourth week and the increase in plasma ghrelin concentration. The author concluded that these findings could explain the alteration of food intake in this setting [13]. The same group further described exaggerated post-prandial suppressive response to ghrelin associated with decreased food intake (50%) in a group of patients after a coronary bypass. At the end of their hospitalisation, patients had an average loss of 4% in body weight as well as a decrease of 5% in arm circumference [14]. Similar findings were recently reported [15] even though no association between the circulating levels of ghrelin and gastric emptying was found.

21.1.1.2 Prandial Phase (Actual Food Intake)

Physiology

Swallowing is a sensory-motor activity that occurs every minute to manage saliva and dozens of times during a meal to ensure hydration and nutrition. It must be functional at birth.

There are three phases in swallowing:

- *Oral phase*: This phase requires integrity and functionality of the lips, tongue and jaw muscles. During this phase, pleasure is developed through the stimulation of taste buds and olfactory receptors. The duration of this phase depends on the type of food as well as hunger, motivation and environment. The oral phase ends when the bolus passes the velum pillars.
- *Pharyngeal phase*: This is a reflex phase corresponding to the time taken by the bolus to move from the oropharyngeal isthmus to the upper sphincter of the oesophagus. This is the most critical phase of swallowing, where the bolus moves through the aero-digestive junction. This phase is comparable to a 0.75 s apnoea. However, it may be longer in the case of solid foods sphincter opening. In awake subjects, 80% of the swallowing occurs during expiration in respiratory cycle.
- *Oesophageal phase*: This phase ensures the transfer of food from the upper sphincter of the oesophagus to the cardia, with a peristaltic wave that travels up and down the oesophagus.

Swallowing Disorders During Critical Illness

In the ICU, the incidence of swallowing disorders or dysphagia is variable. A meta-analysis reported an incidence ranging from 3% to 62% of patients after extubation. This variability was due to the heterogeneity of the population included (i.e. patients after a stroke or not) as well as the methods used to assess swallowing disorders (clinical or instrumental) and the moment chosen for patient evaluation (days 1, 2, 5, etc.) [16]. More recently, a multivariate analysis of retrospective study including 446 patients without neurological impairment has showed that an intubation period of more than 7 days was an independent predicting factor for moderate or severe dysphagia. Also, dysphagia was a predictor of pneumonia, re-intubation and mortality in hospital. One hundred seventy-nine patients had moderate to severe dysphagia, and 132 (74%) had no oral nutrition. Ninety-eight patients (55%) left the hospital with dysphagia, and 26 (15%) patients were discharged from hospital with a gastrostomy [17].

Another retrospective study including 254 patients after cardiac surgery with prolonged intubation has showed an incidence of 51% for dysphagia. The average time before oral feeding was started was 76 h after extubation. Eighty-six patients (33%) started oral nutrition within the first 24 h post extubation. The average length of mechanical ventilation and dysphagia were described as independent factors causing a delay in food intake. Dysphagia is also an independent factor increasing average length of stay in hospital [18]. On a physiopathological point of view, post-intubation swallowing dysphagia has appeared to be multifactorial, depending on laryngeal mucosal lesions, inflammation and oedema, uni- or bilateral vocal cord immobility, insufficient closure of the larynx during swallowing or muscle atrophy during intubation [16]. Some authors have shown that the swallowing reflex is delayed in post-intubation. Lag time is lengthened and the reflex is triggered with a delay [19]. This has been proven to be due to an alteration of chemoreceptors and mechanoreceptors located in the mucosa in contact with the endotracheal tube [20].

21.1.1.3 Post-prandial Phase (Satiety)

Physiological Regulation

Control of food intake depends on neurological and hormonal signals. Ingesting food induces gastric and intestinal mechanoreceptors to respond via the vagus nerve. Chemoreceptors, also present at the gastrointestinal level, are sensitive to different nutrients (carbohydrates, lipids and peptides). These signals are routed to the solitary nucleus in the brainstem and integrated along with visceral signals and sent to the hypothalamus.

Post-prandial Disorders of the Critically Ill

Impairment in gastric emptying is also common during critical illness, although it can be partially prevented by an early initiation of enteral feeding in patients unable to eat. A role of gut-derived hormones has also been hypothesised to explain these alterations. Many hormones of gut-brain axis are involved in energy and metabolic regulation; some of them are studied in intensive care. Cholecystokinin (CCK) and PYY secreted by the gut have an anorectic effect, play a role in GI motility [21] and are both increased in ICU patients [13, 21, 22].

Gastrointestinal symptoms of ICU patients may contribute to the reduction in food intake. Symptoms such as nausea, vomiting, bloating, diarrhoea and constipation will cause a discomfort that may hinder oral nutrition. A prospective observational study over 3 years evaluated gastrointestinal symptoms in ICU patients. One thousand three hundred seventy-four patients were included, 775 (59.1%) had at least one gastrointestinal symptom and 475 (36.2%) had more than one symptom during the ICU stay. In this group of patients, 501 (38.2%) had nausea and vomiting, 184 (14%) diarrhoea and 139 (10.6%) abdominal bloating. The presence of digestive symptoms was an independent predictor of mortality in intensive care units [23].

21.1.2 Practical Attitudes

21.1.2.1 Selecting Patients

Probably, the first point in such a strategy is selecting those patients who can be safely fed orally such as patients without swallowing disorders. Oral intake can be risky in case of preexisting swallowing disorders, stroke, exacerbation of neuromuscular disease (myasthenia gravis, muscular dystrophy, Guillain-Barré syndrome, ALS or myotonia), neurosurgical patients undergoing oncological treatment, severe traumatic brain injury, surgery of the aerodigestive junction, radiotherapy or chemotherapy. In these patient groups, long-term enteral access is commonly required [24].

21.1.2.2 Conditions for Food Intake

Certain conditions are needed before trying food intake: for a conscious patient who responds to simple commands, time allowed between extubation and food intake is variable and should be subject to case-to-case assessment. In general practice, a period of 12–24 h without ventilation should be respected [18]. At the same time, we must achieve hemodynamic and respiratory stability, with low doses of vasoactive amines and oxygen [25].

21.1.2.3 Swallowing Test

The atmosphere around the meal should be calm; avoid talking during food intake. The person feeding the patient should be facing the patient. Hot or cold foods, spices or flavoured fizzy drinks will stimulate positively intraoral sensitivity.

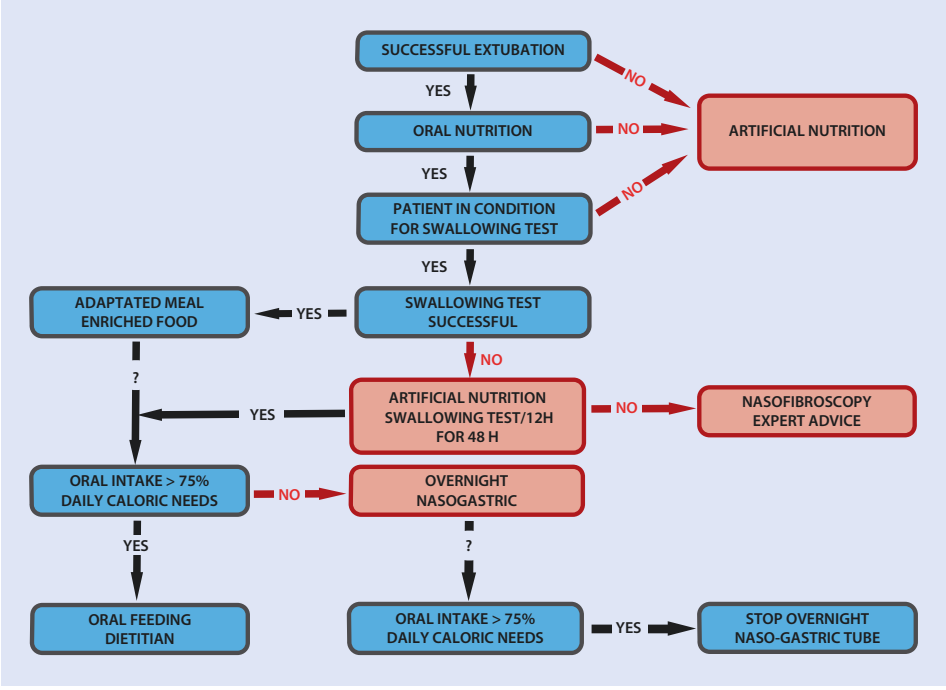
Postures are important when starting the swallowing test. We suggest that the patient should be sitting up straight with his head bowed to the ground and use a small spoon and no straw. You can use products with mixed consistency (flan or mash) as these have proven to be no more dangerous than liquids [26]. One study has shown that 90 ml of water is a good test to start oral nutrition [27]. If after the 90 ml of water there are no signs of inhalation, a specific diet can be started without fear for additional complications [28]. You should suspect dysphagia and inhalation in case of coughing, multiple swallowing, odynophagia, drooling, nasal reflux, choking or a tearful voice. Negative tests for swallowing can be made once or twice a day. If they are still negative after 48 h, seek expert advice for a nasofibroscopy. Preemptive swallowing stimulation before extubation decreased the rate of swallowing disorders from 50% to 27% [29].

21.1.2.4 Food Management

The dietitian looks mainly for food aversions and asks for the family's opinion on composing the meal tray. Family involvement can be of significant help. First, it has been shown that participation in care increases satisfaction and decreases anguish and anxiety [30]. Azoulay et al. have shown that 76% of patients wanted the participation of relatives in routine care and 70% wanted their relatives to be involved in their diet [30]. Active family participation improves food intake for groups of HIV and diabetic patients [31, 32]. Families can contribute positively to mealtime on a social level by bringing food that the patient wants and that is not available in hospital kitchens [33]. Restrictive diets must be avoided in the ICU (diabetic, salt-free, lipid-lowering, etc.) except in some cases (food allergy, malabsorption). At the same time, regular pain assessment must be made considering that patients with pain were observed to eat very little food at mealtimes [34]. The hospital's pain centre may even be asked to make a proper evaluation and therapy. Some patients have psychotropic medication before ICU admission (antidepressants, anxiolytics, etc.), and the absence of contraindications must be assessed before their readministration. Nausea and vomiting should be carefully managed and should be treated with metoclopramide with follow-up. Constipation should also be monitored and treated where necessary. Ionic modifications must be corrected (natremia, phosphoremia, magnesemia or kalemia) as well as glycaemic changes using standard protocols.

The choice of food must be positive (by taste and not by aversion). The patients must have a list of meals available to choose from. Monotony is a frequent source of undernutrition. If possible, within staffing constraints, patients should be asked at what time they prefer eating. ICU patients are mostly undernourished [24]. Oral refeeding must be the best possible right from admission to ICU. The three main meals should be enriched with calories and proteins without increasing the overall volume. Palatability should be increased by adding butter, oil, whole milk pods, grated cheese, sugar, chestnut cream and honey. Oral nutritional supplements in addition to meals such as snacks and outside meals are to be encouraged (2 h before or after). They must be adapted to the patient's taste and ability to swallow (soups, creams, juices, neutral products, cereals, dairy liquids, cakes and protein powder). In the first 24–48 h, the dieticians must make an accurate assessment of the quantities eaten. If caloric and protein intake per day is less than 75% of estimated

needs [35], supplemental enteral nutrition may be indicated via a thin tube (Fr/CH 8-10, 120 cm), thereby allowing oral intake and communication without increasing the risk of inhalation. Alternatively, an enteral access via gastrostomy or jejunostomy can be inserted. The enteral nutrition formula can be administered overnight without having a negative effect on hunger and satiety [36]. This nutrition supplement should be maintained until the patient manages to consume at least 70% of recommended intake.



21.1.3 Priorities for Future Research

As stated before, involvement of families in care (food intake in the specific) may become crucial for critical patient recovery. The development of programmes including families on care may improve treatment overall load [37]. Therefore, the respect of cultural and religious diversity of our patients and their families should become a priority of care in the ICU [38]. Regardless of origin and religion beliefs, human beings must be considered equal and free.

The use of intravenous ghrelin analogues has been effective in cancer patients with the result of increasing food intake and appetite [39, 40]. In COPD patients, the administration of intravenous ghrelin twice a day for 3 weeks improves muscle strength as demonstrated by the 6-min walk test and spirometric parameters [41]. The same team has also shown positive results in patients with congestive heart failure [42].

It is important to note that some of the anabolic effects of ghrelin are due to stimulated secretion of growth hormone (GH) [43]. However, the effect of GH secretion remains to be carefully verified as the administration of GH has been proven to increase mortality in ICU [44].

21

Also, future physiologic studies of the brain gut axis in ICU need to be carried out to establish the basic levels and the role of certain hormones such as motilin, GLP-1 and GLP-2.

Some teams have worked on the effect of exercise in ICUs on a metabolic and functional level.

Conclusion

Food intake in the ICU is even more complex than outside the ICU environment since several factors play a role. Currently, intensive care medical literature and experience is too poor to help in daily practice. Even the nutritional management of certain groups of patients who are not intubated during their ICU stay, such as patients undergoing high-flow oxygen therapy and patients on non-invasive ventilation [45], does not follow international recommendations. Future research is expected in this field. In the meantime, improving meals and food intake will come from multidisciplinary teamwork and communication with all downstream wards. Obtaining feedback on the patients' development in rehabilitation centres and their social reintegration are key factors in improving our practices.

Take Home Messages

- Food intake in intensive care is not codified and is very important in the rehabilitation phase.
- Management must be multimodal and multi-disciplinary.
- The contact with the rehabilitation departement is important for the feedback and the improvement of the care.

References

1. Brame AL, Singer M. Stressing the obvious? An allostatic look at critical illness. Crit Care Med. 2010;38(10 Suppl):S600–7.
2. Merriweather J, Smith P, Walsh T. Nutritional rehabilitation after ICU – does it happen: a qualitative interview and observational study. J Clin Nurs. 2014;23(5–6):654–62.
3. Hill AJ, Magson LD, Blundell JE. Hunger and palatability: tracking ratings of subjective experience before, during and after the consumption of preferred and less preferred food. Appetite. 1984;5(4):361–71.
4. Deane A, Chapman MJ, Fraser RJL, Horowitz M. Bench-to-bedside review: the gut as an endocrine organ in the critically ill. Crit Care Lond Engl. 2010;14(5):228.
5. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001;50(8):1714–9.
6. Cutler LR, Hayter M, Ryan T. A critical review and synthesis of qualitative research on patient experiences of critical illness. Intensive Crit Care Nurs. 2013;29(3):147–57.
7. Jubran A, Lawm G, Kelly J, Duffner LA, Gungor G, Collins EG, et al. Depressive disorders during weaning from prolonged mechanical ventilation. Intensive Care Med. 2010;36(5):828–35.
8. Schiffman SS, Zervakis J. Taste and smell perception in the elderly: effect of medications and disease. Adv Food Nutr Res. 2002;44:247–346.
9. Ito K, Kohzuki M, Takahashi T, Ebihara S. Improvement in taste sensitivity following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. J Rehabil Med. 2014;46(9):932–6.
10. Schiffman SS. Critical illness and changes in sensory perception. Proc Nutr Soc. 2007;66(3):331–45.
11. Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2002;30(11):785–92.

12. Schiffman SS, Warwick ZS. Use of flavor-amplified foods to improve nutritional status in elderly patients. Ann N Y Acad Sci. 1989;561:267–76.
13. Nematy M, O'Flynn JE, Wandrag L, Brynes AE, Brett SJ, Patterson M, et al. Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study. Crit Care Lond Engl. 2006;10(1):R10.
14. Nematy M, Brynes AE, Hornick PI, Patterson M, Ghatei MA, Bloom SR, et al. Postprandial ghrelin suppression is exaggerated following major surgery; implications for nutritional recovery. Nutr Metab. 2007;4:20.
15. Santacruz CA, Quintairos A, Righy C, Crippa IA, Couto L, Imbault V, et al. Is there a role for enterohormones in the gastroparesis of critically ill patients? Crit Care Med. 2017;45(10):1696–701.
16. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest. 2010;137(3):665–73.
17. Macht M, Wimbish T, Clark BJ, Benson AB, Burnham EL, Williams A, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. Crit Care Lond Engl. 2011;15(5):R231.
18. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. Can J Surg J Can Chir. 2009;52(2):119–24.
19. de Larminat V, Montravers P, Dureuil B, Desmonts JM. Alteration in swallowing reflex after extubation in intensive care unit patients. Crit Care Med. 1995;23(3):486–90.
20. Brodsky MB, Gellar JE, Dinglas VD, Colantuoni E, Mendez-Tellez PA, Shanholtz C, et al. Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. J Crit Care. 2014;29(4):574–9.
21. Beglinger C, Degen L, Matzinger D, D'Amato M, Drewe J. Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans. Am J Physiol Regul Integr Comp Physiol. 2001;280(4):R1149–54.
22. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003;349(10):941–8.
23. Reintam A, Parm P, Kitus R, Kern H, Starkopf J. Gastrointestinal symptoms in intensive care patients. Acta Anaesthesiol Scand. 2009;53(3):318–24.
24. Massanet PL, Petit L, Louart B, Corne P, Richard C, Preiser JC. Nutrition rehabilitation in the intensive care unit. JPEN J Parenter Enteral Nutr. 2015;39(4):391–400.
25. McClave SA, Dryden GW. Critical care nutrition: reducing the risk of aspiration. Semin Gastrointest Dis. 2003;14(1):2–10.
26. Lee KL, Kim WH, Kim EJ, Lee JK. Is swallowing of all mixed consistencies dangerous for penetration-aspiration? Am J Phys Med Rehabil. 2012;91(3):187–92.
27. DePippo KL, Holas MA, Reding MJ. Validation of the 3-oz water swallow test for aspiration following stroke. Arch Neurol. 1992;49(12):1259–61.
28. Leder SB, Suiter DM, Warner HL, Kaplan LJ. Initiating safe oral feeding in critically ill intensive care and step-down unit patients based on passing a 3-ounce (90 milliliters) water swallow challenge. J Trauma. 2011;70(5):1203–7.
29. Hwang CH, Choi KH, Ko YS, Leem CM. Pre-emptive swallowing stimulation in long-term intubated patients. Clin Rehabil. 2007;21(1):41–6.
30. Azoulay E, Pochard F, Chevret S, Arich C, Brivet F, Brun F, et al. Family participation in care to the critically ill: opinions of families and staff. Intensive Care Med. 2003;29(9):1498–504.
31. Serrano C, Laporte R, Ide M, Nouhou Y, de Truchis P, Rouveix E, et al. Family nutritional support improves survival, immune restoration and adherence in HIV patients receiving ART in developing country. Asia Pac J Clin Nutr. 2010;19(1):68–75.
32. Watanabe K, Kurose T, Kitatani N, Yabe D, Hishizawa M, Hyo T, et al. The role of family nutritional support in Japanese patients with type 2 diabetes mellitus. Intern Med Tokyo Jpn. 2010;49(11):983–9.
33. De Castro JM. How can eating behavior be regulated in the complex environments of free-living humans? Neurosci Biobehav Rev. 1996;20(1):119–31.
34. Merriweather JL, Salisbury LG, Walsh TS, Smith P. Nutritional care after critical illness: a qualitative study of patients' experiences. J Hum Nutr Diet Off J Br Diet Assoc. 2016;29(2):127–36.
35. Kondrup J. Can food intake in hospitals be improved? Clin Nutr. 2001;20:153–60.
36. Stratton RJ, Stubbs RJ, Elia M. Short-term continuous enteral tube feeding schedules did not suppress appetite and food intake in healthy men in a placebo-controlled trial. J Nutr. 2003;133(8):2570–6.
37. Dowling J, Vender J, Guilianelli S, Wang B. A model of family-centered care and satisfaction predictors: the critical care family assistance program. Chest. 2005;128(3 Suppl):81S–92S.

38. Høye S, Severinsson E. Multicultural family members' experiences with nurses and the intensive care context: a hermeneutic study. Intensive Crit Care Nurs. 2010;26(1):24–32.
39. Neary NM, Small CJ, Wren AM, Lee JL, Druce MR, Palmieri C, et al. Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2004;89(6):2832–6.
40. Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, Ghatei MA, et al. Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. J Am Soc Nephrol JASN. 2005;16(7):2111–8.
41. Nagaya N, Itoh T, Murakami S, Oya H, Uematsu M, Miyatake K, et al. Treatment of cachexia with ghrelin in patients with COPD. Chest. 2005;128(3):1187–93.
42. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, Shimizu W, et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation. 2004;110(24):3674–9.
43. Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A, Harada M, et al. Ghrelin strongly stimulates growth hormone release in humans. J Clin Endocrinol Metab. 2000;85(12):4908–11.
44. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999;341(11):785–92.
45. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. Crit Care Lond Engl. 2017;21(1):293.

Follow-Up Consultations: Why?

Evelyn J. Corner and Stephen J. Brett

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_22

Learning Objectives

- To understand the history of ICU follow-up clinics
- To understand the need for, and potential benefits of, ICU follow-up clinics
- To understand the current literature into the effects of ICU follow-up consultation

22

22.1 Introduction and the History of ICU Follow-Up

The intensive care unit can often seem like some form of technologically dominated citadel at the centre of the hospital; so how is it that the practice of intensive care medicine has come to be involved in the long-term care and rehabilitation of survivors, even after they have been discharged from hospital? The origin of this seems lodged several decades ago with colleagues from an internal medicine (rather than anaesthesiological) background that were reviewing patients after discharge in their own medical outpatient departments. They observed that many patients seem to be struggling with certain aspects of their recovery [1]. Perhaps previously, intensive care clinicians had waived the patients through the exit door of the unit anticipating a fairly trouble-free recovery back to something very close to their premorbid level of existence. However, what these colleagues noticed was that for many people leaving, the intensive care unit seems to be the start of a journey, rather than the end of one [2].

So why should this have been a novel finding? Well, it is possible that clinicians who were receiving discharged intensive care patients into their medical or surgical services were simply not seeing sufficient numbers to identify patterns of difficulty experienced by many patients. As multiorgan failure is one of the highest risk factors for aggressive muscle wasting [3], perhaps the majority of the sickest 'at-risk' patients did not survive to fall victim to the long-term consequences of critical illness [4]. Possibly, clinicians were not focused on issues not necessarily in their primary field of interest. Perhaps, the contribution of colleagues in the therapy professions was not as prominent or valued as it is today, or indeed the focus of physiotherapists in particular was towards respiratory care, and not rehabilitation orientated.

However, extremely observant clinicians began to notice patterns of difficulty experienced in the patients that they were seeing. In response to this, exploratory studies were established to challenge the notion that recovery was a straightforward thing for the majority of patients. These early studies seem strikingly prescient in that they identified many of the elements of what is now described as the post-intensive care syndrome [5–10]. Specifically, patients were weak and appeared to have lost significant muscle mass; there was early fatigue in tasks which had previously not seemed challenging; they had lost cardiovascular endurance, as well as confidence in their ability to perform their own activities of daily life; and a variety of other physical complaints ranging from sexual dysfunction, to joint stiffness, to persisting breathlessness are outlined in detail in Part I of this book.

In addition, there appeared to be patterns of non-physical difficulty observed including anxiety, depression, and the symptoms of post-traumatic stress disorder in some [11, 12]. Along with these observations developed an appreciation that for many individuals the memories of their time in the intensive care unit were strange, sometimes troubling, and formed a fundamental backdrop to their recovery [13]. A further key observation was that the experience of intensive care could be part of a very *negative* life

experience or, for some, something more positive. This can be related to the discrepancy between our realities and our expectations [14], for example, a young person experiencing a major road traffic accident will tend to view their whole experience as a negative change in health status, and this will be the prism through which they will view their recovery. By contrast, an elderly person recovering from an a aortic valve replacement for a disease which had rendered their life intolerable due to breathlessness and chest pain may view their recovery somewhat differently, in that their life is no longer dominated by the pre-surgical symptoms, and thus they may feel the whole thing has been something of a *positive* experience. Occasionally, patients who have come through a critical illness or survived major trauma will exhibit *post-traumatic growth*, a phenomenon of increased positivity exhibited by some after surviving a serious challenge; this is characterised by reappraisal of one's life and priorities, better body awareness, and development of oneself [15]. The recognition of the complex collection of symptoms experienced by ICU survivors led to the implementation of the ICU follow-up clinic within clinical practice, not just a research setting. Diagram one displays the typical elements that may form important factors in an ICU survivor's recovery (Fig. 22.1).

The optimum model of intensive care follow-up has yet to be established, and the delivery of ICU follow-up is consistent between centres and countries [16]. In the United Kingdom, the delivery of ICU follow-up was audited in 2006, and at that time

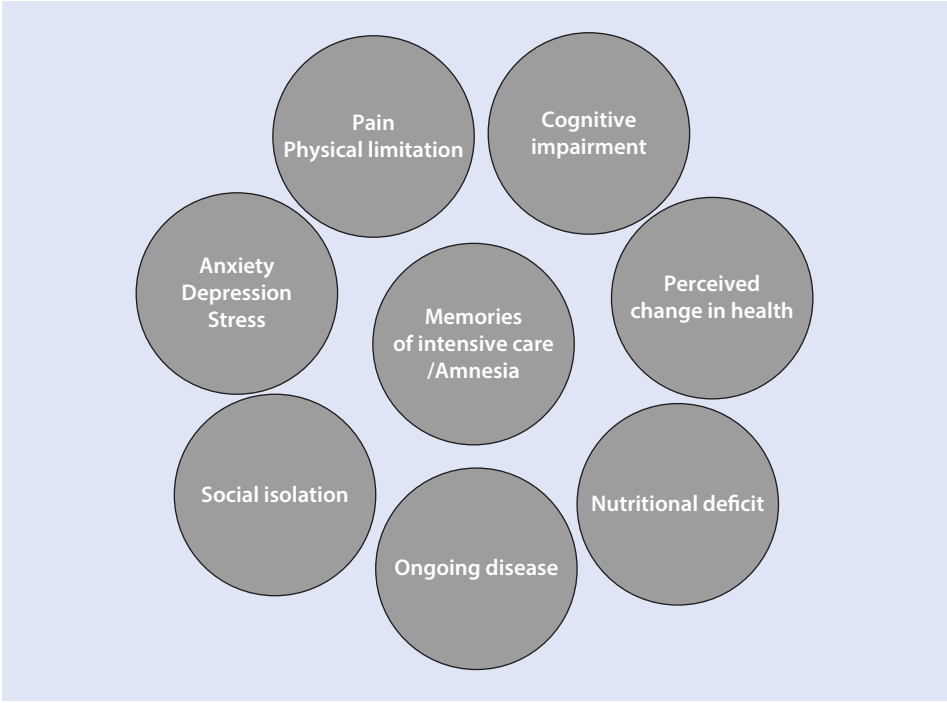


Fig. 22.1 Typical elements may come from important factors in an ICU survivor's recovery depicted as an "exploded" Venn diagram. How these elements link up and interact for an individual, and the relative importance of each, seems impossible to predict. Important external factors may conceivably be the presence of family support and continuing health and social care input

around 25% of Intensive Care Units had some form of follow-on service [17]. Since then, the recommendations on rehabilitation after critical illness published by the National Institute for Health and Care Excellence (NICE) (Clinical Guideline 83, 2009) [18] and the subsequent NICE Quality Standards for Rehabilitation after Critical Illness (2017) [19] have been published. Both of these documents stipulate that patients should be assessed at 3 months after discharge for quality of recovery and future rehabilitation needs; however, no recommendations were made on how this could be achieved. A subsequent survey of NICE CG83 implementation in 2014 showed that despite this clinical guidance, ICU follow-up was still only offered in 27% of UK Intensive Care Units [20]. It is currently unclear how widespread these recommendations have been adopted.

In addition, published studies of intensive care follow-up clinics have failed to demonstrate a measurable benefit in health-related quality of life, depression, anxiety, return to employment, physical problems, or cost-effectiveness but may have a positive effect on PTSD [21, 22]. Of note, numbers of interventional studies in ICU survivors, such as post-ICU rehabilitation, have also failed to demonstrate a measurable benefit [23–25]. In some however, a convergent mixed methods approach has been taken with *qualitative* analyses running in parallel. These studies have shown that patient satisfaction and engagement with the recovery process seem to be higher in the arm of the trial more intensively managed [26, 27]. This suggests that perhaps some of the literature may have either not had the correct model of intervention or alternatively had selected outcome measures that were simply unresponsive to any change and/or had significant floor and ceiling effects. Thus, the evidence base behind delivering benefit through an intensive care follow-up service remains patchy at best.

Work done with patient and carer groups has repeatedly identified that the steps down from a very high to very low intensity model of care is a source of great uncertainty and anxiety, often labelled as 'relocation stress' in the literature; patients and family members feel insecure in what the rehabilitation plan should be, and the communication of this plan is often interrupted by transfers [28]. In an effort to improve this, even in the absence of an evidence base, the UK Health Service has introduced mandatory quality standards concerning the development, documentation, and communication of multidisciplinary rehabilitation plans for particularly vulnerable groups [19]. Logically, it seems possible that these may improve individuals' recovery and their engagement and motivation may be supported by such arrangements. One early interventional study, which demonstrated a signal for improvement, involved a self-directed rehabilitation manual, which was delivered to patients as they left the hospital [29]. However, it was felt that the support of the intensive care team was essential to the success of this particular venture.

22.2 What Have Follow-Up Clinics Taught Us So Far?

There is no doubt that the evolution of intensive care in clinics and the opportunity to conduct research based in such clinics have provided a window onto the experiences of patients recovering from critical illness [30]. However, there are some caveats that need to be stated before overly extrapolating research derived from intensive care clinics. There is often an appreciable 'lost to follow-up' rate from the original target populations identified within an intensive care setting. Often, only a fraction of this population ends up being

reported on in detail. The reasons why one individual might chose to attend a clinic (whether or not there is a study involved) and another chose not to attend are impossible to ascertain. This leads to a major unquantifiable risk of enrolment bias, and thus the true prevalence of particular conditions in the survival population is often hard to ascertain. This is particularly apparent with post-traumatic stress disorder (PTSD) where an honest attempt to identify the relevant literature and produce an estimate of the prevalence of PTSD was undermined by differing estimates within the literature [31]. One excellent example of a more robust study was published by Dr Wade and co-authors who identified patients within intensive care and established such a personal relationship with them that the patients' loyalty to the investigators and the study was so strong that the dropout rate was extremely low [32]. This gave far more convincing estimates of prevalence rates for psychological problems.

The range of physical consequences reported which are dealt with in detail in other chapters include a loss of skeletal muscle [3], with associated impairment of functional status [4–7], loss of appetite and nutritional impairment, stiff joints, and a myriad of other complaints, ranging from damage to the upper airway to hair loss [2]. From the point of view of non-physical consequences, there are multiple reports of persisting cognitive impairment, along with a burden of anxiety and depression and in some post-traumatic stress symptoms and frank post-traumatic stress disorder [11, 12]. In addition, studies have also identified that many individuals, once discharged home, require substantial assistance from those around them to live securely in a non-hospital environment. The family members frequently become enrolled as informal caregivers, and this can have adverse consequences for their own lives, as well as the family unit more broadly [9]. Importantly, the financial resilience of the family can be unsettled, and family financial security and employment can be adversely affected by duties as informal caregivers; this seems particularly the case for the self-employed and those running small businesses [1, 2].

22.3 The Need for ICU Follow-Up

Those admitted to critical care can have vastly different underlying diagnoses; they are a notoriously heterogeneous group. Some of the 'speciality' patient populations have recognised long-term rehabilitation needs and hence fall under established care pathways. Examples include stroke survivors who (in the United Kingdom) are a priority patient group for community rehabilitation services [33]; cardiology/cardiothoracic patients who have a structured cardiac rehabilitation programme, which in the United Kingdom is supported by British Heart Foundation (BHF) trained fitness instructors long term (▶ www.bhf.org.uk); and Chronic Obstructive Pulmonary Disease (COPD) patients, who usually fall under a structured programme of pulmonary rehabilitation and follow up with their respiratory physicians [34]; but what about the 'non-specialist' patient populations? Those with no recognised 'chronic health condition' – pneumonia, flu, and bowel perforation, to list a few. These patients had not traditionally been recognised as having a 'chronic condition', and as such no care pathways had been in existence. However, research into ICU follow-up has taught us that these patients do have chronic health needs, which can present in a multitude of ways; these are outlined in detail in part I and part II of this book. In fact, some of these specialised rehabilitation pathways are not necessarily optimum for

longer staying ICU survivors; for many such patients, the issues which come to dominate the latter stages of their ICU stay and their future recovery are more about 'chronic critical illness', rather than their admitting diagnosis. Thus, services need to be sensitive to these needs, rather than simply say confidence building in a post-myocardial infarction cardiac rehabilitation service.

These patients historically fall through the cracks of community services, exacerbating the sense of relocation stress; in the absence of responsive community-based services, ICU follow-up clinics are their safety net. Even for those under established care pathways, they allow identification and management of the specific issues prevalent in the ICU group, such as PTSD, which may not be assessed routinely. Although the quantitative measures of the impact of follow-up clinics have shown little impact, qualitatively, this coordinated approach to care demonstrates much better patient satisfaction than routine care.

22.4 Current International Practice

The delivery and provision of ICU follow-up is variable between centres and geographical locations. Some will offer a self-help manual for the patients to work through by themselves [35]. Others offer a staged approach to follow-up, with the provision of a patient diary at ICU discharge, ward follow-up from ICU staff, and then outpatient review between 6 weeks and 12 months after discharge [36], whereas some centres will have a one off follow-up at around 6–12 weeks. These can be nursing led or multidisciplinary led [35].

The optimal method of delivery is yet to be established. A Dutch expert consensus statement recommends nurse-led follow-up as one between 6 and 12 weeks after ICU discharge to screen for physical, psychological, and cognitive needs [37]. However, nonattendance rates for these types of clinics can be high at up to 31% [38], and such a system may not practically work in hospitals with wide catchments areas, such as Australia or the United States [38]. Adequate funding to provide these services can also be problematic, especially the absence of quantitative evidence base.

Further detail on the feasibility and structure of follow-up clinics can be found in ► Chaps. 23 and 26.

22.5 Patient Experience of ICU Follow-Up Clinics

Work to explore the patient experience of follow-up clinics has identified that they can play a key role in the filling in of life narrative that has been lost due to amnesia. This can help patients to process and make sense of their experiences allowing them to move on [39]. This is particularly useful for patients whose partners struggle to talk about their time on ICU due to their own psychological distress; follow-up clinics for relatives has been suggested in view of this and may be of benefit [38].

Additionally, follow-up clinics provide an opportunity for patients and relatives to clarify information and advice. While many patients are given the option to contact their ICU teams to discuss their concerns after their discharge, some survivors have reported feeling uncomfortable disrupting busy clinicians. Follow-up clinics provide a structured

forum to discuss concerns with the ICU staff members who cared for them [39]. This reunion and continuity of care is valued by patients, and on-going specialist monitoring is often reassuring. Conversely, follow-up clinics also provide an opportunity for patients to feedback to the ICU staff about their experiences, which, if acted upon, could help to improve care for future patients [39]. Of note, follow-up clinics that include a visit to the ICU should be well planned and done with caution, as there is a risk of further distress if returning to the actual ICU environment [40].

Follow-up clinics can also help patients to manage their expectations regarding recovery. Critical care survivors, on the whole, will not have been in this situation before, which means that they have no yardstick to monitor their progress and expectations against. Knowing what is 'normal' or to be expected in terms of recovery milestones and timeframes reassures both patients and relatives [40]. This is best delivered by expert clinicians whom they trust and who know their history.

ICU follow-up also provides an opportunity for onward referral to specialist rehabilitation services, with between 7% and 50% [38] of ICU follow-up consultations leading to onward referral.

22.6 The Future of ICU Follow-Up?

The evidence that many ICU survivors experience long-term consequences of critical illness seems secure. Less secure, and somewhat circumstantial, is the evidence that following such patients up, and providing care based from within the critical care team delivers benefit, even though this is intuitively appealing. Convenience and responsiveness are important [9], and many patients do not find repeated hospital attendances attractive, but even well-developed generic community-based support may lack the knowledge of critical illness needed to support people in detail. Communication and information have been highlighted repeatedly as important enablers. Whether generic community support can be leveraged with carefully co-designed website-based help (e.g. ► http://www.criticalcarerecovery.com) has yet to be fully evaluated.

What services are available in an individual community is clearly a very local, but crucial, issue. Thus, attempting to identify some globally applicable optimum service model seems a potentially futile exercise. Perhaps, effort might be more usefully expended on identifying the exact *elements* of a holistic enhanced rehabilitation programme that would be beneficial and leaving delivery model to local people. The elements of such a programme are likely to include attention to physical re-enablement, psychological and motivational support, and nutritional optimisation; studying these as isolated interventions may not be successful, as they are likely to interact significantly. Thus, combination packages of therapy may need to be studied as *complex interventions*; this is difficult science, and careful thought will be needed to ensure future studies are designed with outcome measures that are more likely to be sensitive to patient-centred and important change, while recognising that recovery is likely to be non-linear, and what is considered important to the patient may fluctuate and change as they progress and adapt to new disability [41]. On-going work to identify core outcomes for critical care may assist in the process (► http://www.comet-initiative.org). We may have to compromise on our reductionist enthusiasm for understanding detailed cause and effect for the general benefit of our patients and their families.

Conclusion

Although critical illness starts with an acute event that often strikes suddenly and without warning, follow-up studies of critical care patients have clearly taught us that it ends less abruptly, with lingering consequences, and can shape the rest of their life – for better or for worse. It may be pragmatic to consider recovery from critical illness in two stages: *resuscitation* followed by *rehabilitation*. This rehabilitation stage is likely to be turbulent and non-linear with patients reporting accounts of fragmented care and insufficient support services. Follow-up consultation, although lacking a quantitative evidence base, may provide a safety net for critically ill patients whose needs may slip between the cracks of healthcare services. The opportunity to talk to staff, to explore what they have been through with those who truly understand it, and to fill in gaps in memory and therefore life narrative can help patients move on and reconstruct a compelling future.

Take Home Messages

- Critically ill patients can develop significant physical and psychological morbidity that can dictate their course of recovery and lead to a turbulent journey of rehabilitation and reintegration of life outside the ICU.
- ICU follow-up clinics have helped to elucidate the complex problems that critical care survivors experience, establishing chronic care needs as fundamental to recovery from critical illness.
- Evidence to support ICU follow-up has shown little demonstrable quantitative benefit in terms of addressing both physical and psychological problems, although it may be beneficial to sufferers of PTSD.
- However, qualitatively, the research suggests that ICU follow-up is beneficial; supporting transitions of care, filling in of lost life narrative, and improving patient satisfaction. The delivery of ICU follow-up, by ICU clinicians, seems to reassure patients, and meeting the team who cared for them can help patients move on.
- Research into ICU follow-up is hampered by selection bias and potentially insufficiently sensitive core outcomes.

References

1. Griffiths R, Jones C. ABC of intensive care: recovery from intensive care. Clinical review. BMJ. 1999;219:427–9.
2. Broomhead LR, Brett SJ. Clinical review: intensive care follow-up – what has it told us? Review. Crit Care. 2002;6(5):411–7.
3. Puthucheary ZA, Rawal JR, McPhail M, Connolly B, Ratnayake G, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
4. Kaukonen K-M, Bailey M, Suzuki S. Mortality related to severe sepsis and septic shock among critically ill patient in Australia and New Zealand, 2000–2012. JAMA. 2014;311(13):1308–16.
5. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683–93.
6. Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matté A, Barr A. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006;174(5):538–44.
7. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364:1293–304.

8. Ramsey P, Huby G, Rattray J, Salisbury LG, Walsh TS, Kean S. A longitudinal qualitative exploration of healthcare and informal support needs among survivors of critical illness: the RELINQUISH protocol. BMJ Open. 2012;2:e001507.
9. Griffiths J, Hatch RA, Bishop J, Morgan K, Jenkinson C, Cuthbertson B, et al. An exploration of social and economic outcome and associated health related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013;17:R100.
10. Quinlan J, Gager M, Fawcett D. Sexual dysfunction after intensive care. Br J Anaesth. 2001;87:348.
11. Pandharipande P, Girard TD, Jackson JC, Morandi A, Thompson JL, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306–16.
12. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu J, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med. 2015;43(5):1121–9.
13. Carver CS, Scheier MF. Scaling back goals and recalibration if the affect systems are processes in normal adaptive self-regulation: understanding 'response shift' phenomona. Soc Sci Med. 2000;50: 1715–22.
14. Löf L, Ahlström G. Severely ill ICU patients recall of factual events and unreal experiences of hospital admission and ICU stay – 3 an 12 months after discharge. Intensive Crit Care Nurs. 2006;22(3):154–66.
15. Hefferon K, Grealy M, Mutrie N. Post-traumatic growth and life threatening physical illness: a systematic review of the qualitative literature. Br J Health Psychol. 2009;14(2):343–78.
16. Egerod I, Risom SS, Thomson T, Storli SL, Eskerud RS, et al. ICU-recovery in Scandinavia: a comparative study of intensive care follow-up in Denmark. Norway and Sweden: Intensive and Critical Care Nursing; 2012.
17. Griffiths JA, Barber VS, Cuthbertson BH, Young JD. A national survey of intensive care follow up clinics. Anesthesia. 2006;61(10):950–5.
18. National Institute for Health and Clinical Excellence. Great Britain. Rehabilitation after critical illness Great Britain. Clinical Guideline 83. Available at: www.nice.org.uk; 2009.
19. National Institute of Health and Clinical Excellence. Rehabilitation after critical illness in adults. Quality standard [QS158] Published date: Sept 2017.
20. Connolly B, Douiri A, Steier J, Moxham J, Denehy L, Hart N. A UK survey of rehabilitation following critical illness: implementation of NICE Clinical Guidance 83 (CG83) following hospital discharge. BMJ Open. 2014;4:e004963.
21. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41:763–75.
22. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTiCal study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomized controlled trial. BMJ. 2009;339:b3723.
23. Batterham AM, Bonner S, Wright J, Howell SJ, Hugill K, Danjoux G. Effect of supervised aerobic exercise rehabilitation on physical fitness and quality of life in survivors of critical illness: an exploratory minimized controlled trial (PIX study). Br J Anesth. 2014;113(1):130–7.
24. Walsh TS, Salisbury LG, Merriweather J, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge. The RECOVER randomized controlled clinical trial. JAMA Intern Med. 175(6):901–10.
25. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U, et al. Rehabilitation interventions for post intensive care syndrome: a systematic review. Crit Care Med. 2014;42(5):1263–71.
26. Ramsey P, Huby G, Merriweather J, Salibury L, Rattray J, Griffith D, et al. Patient and carer experience of hospital-based rehabilitation from intensive care to hospital discharge: mixed methods process evaluation of the RECOVER randomized controlled clinical trial. BMJ Open. 2016;6:e012041.
27. Walker W, Wright J, Danjoux G, Howell SJ, Martin D, Bonner S. Project post intensive care eXercise (PIX): a qualitative exploration of intensive care unit survivors' perceptions of quality of life post-discharge and experience of exercise rehabilitation. J Intensive Care Soc. 2015;16(1):37–44.
28. Field K, Prinjha S, Rowan K. 'One amongst many': a qualitative analysis of intensive care unit patients' experiences of transferring to the general ward. Crit Care. 2008;12(1):R21.
29. Jones C, Skirrow P, Griffiths R, Humphris G, Ingleby S, et al. Rehabilitation after critical illness: a randomised controlled trial. Crit Care Med. 2003;31(10):2456–61.
30. Griffiths RD, Jones C. Seven lessons from 20 years of follow-up of intensive care unit survivors. Curr Opin Crit Care. 2007;13:508–13.

31. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Med. 2007;33(9):1506–18.
32. Wade DM, Howell DC, Weinman JA, Hardy R, Mythens MG, Brewin CR. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. Crit Care. 2012;16:R192.
33. Royal College of Physicians. National clinical guideline for stroke. 5th ed. 2016. Available at: www.strokeaudit.org.
34. Hopkinson N, Englebretsen C, Cooley N, Kennie K, Lim M, Woodcock T, et al. Designing and implementing a COPD discharge care bundle. Thorax. 2011;67(1):90–2.
35. Lasiter S. Critical care follow-up clinics: a scoping review of interventions and outcomes. Clin Nurse Spec. 2016;30(4):227–37.
36. Haraldsson L, Christensson L, Conlon L, Henricson M. The experiences of ICU patients during follow up sessions – a qualitative study. Intensive Crit Care Nurs. 2015;31:223–31.
37. Van der Schaaf M, Bakhshi-raiez F, Van der Steen M, Dongelmans DA, De Keizer NF. Recommendation for intensive care follow –up clinics; report from a survey of Dutch intensive cares. Minerva Anesthesiol. 2015;81(2):135–44.
38. Williams TA, Leslie GD. Beyond the walls: a review of ICU clinics and their impact on patient outcomes after leaving ICU. Aust Crit Care. 2008;21:6–7.
39. Prinijha A, Field K, Rowan K. What patients think about ICU follow up services: a qualitative study. Crit Care. 2009;13(2):R46.
40. Haraldsson L, Christensson L, Conlon L, Henricson M. The experience of ICU patients during follow-up sessions – a qualitative study. Intensive Crit Care Nurs. 2015;31(4):223–31.
41. Schwartz CE, Andresen EM, Nosek MA, Krahn GL, the RRTC Expert Panel on Health Status Management. Response shift theory: important implications for measuring quality of life in people with disability. Arch Phys Med Rehabil. 2007;88:529–36.

Feasibility of Follow-Up Consultations

Danielle Heloisa Prevedello and Jean-Charles Preiser

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_23

Learning Objectives

You will learn from this chapter:

- Types of follow-up clinics
- Implementation issues in ICU follow-up
- How to organize an ICU follow-up programme

23

23.1 Introduction

Wider and more sophisticated use of technology in healthcare has reduced intensive care unit (ICU) mortality rates and increased the number of susceptible patients at risk of post-intensive care syndrome (PICS), as described in other chapters of this book [1]. As a result of the rising incidence of PICS, an increasing number of ICU healthcare workers feel concerned by PICS, post-ICU and post-hospital care. In particular, the issues of quality of life and social rehabilitation emerged as public health problems for which intensive care medicine endorses a major responsibility.

The concept of follow-up clinics arose in 1985 in the UK, and in recent years, more clinics of this type have emerged around the world [2]. The general concept is displayed in Fig. 23.1 as the course of an acute illness followed by different steps of follow-up. In the absence of formal standards, each ICU establishes its programme relying on its policies, regulations and resources as defining criteria [3, 4]. The feasibility of the local programmes depends on how models are adapted to local situations, ensuring benefits for patients, health workers, family members and quality of care.

This chapter aims to help ICU practitioners implement follow-up clinics using a systematic and practical approach exhibited in Fig. 23.2.

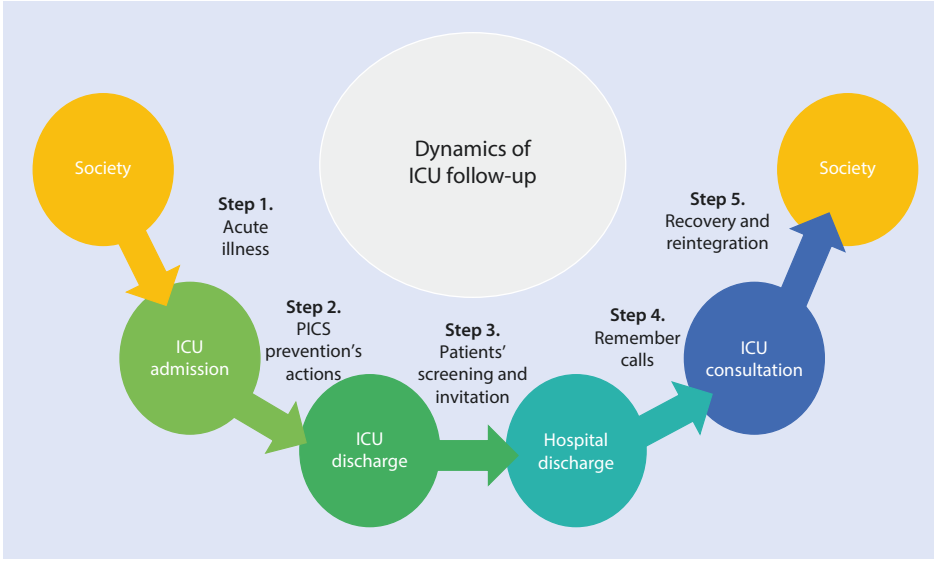


Fig. 23.1 General dynamics of ICU follow-up programme

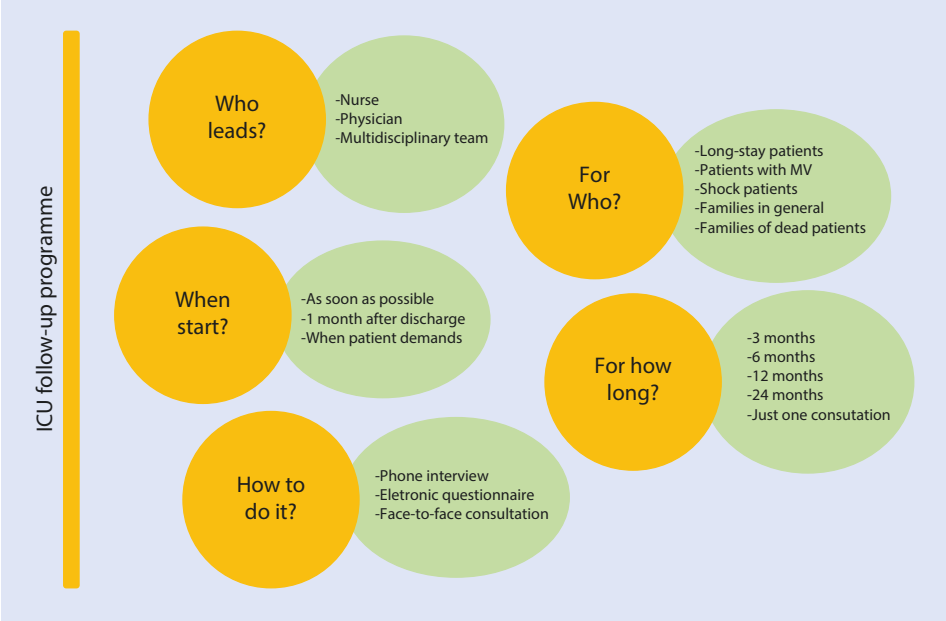


Fig. 23.2 Steps to analysing ICU follow-up in your context

23.2 Types of Follow-up Clinics

The structure of current follow-up clinics established in the USA, Canada, Australia and in some countries in Europe is organized according to different models (Table 23.1). These models can differ in terms of *consultation type, objectives, timing of consultations, interventions and outcomes.*

23.2.1 Consultation Type

Based on published studies, for an ICU follow-up, the consultation type could be a nurse-led programme or a multidisciplinary team-sharing responsibility [5–7]. The lead in a follow-up consultation determines who is responsible for the consultation.

In a nurse-led model, the nurse is in charge of patients' screening, enrolling and evaluation during the consultations [6–8]. The nurses' counsel to the patients allows them to talk about their ICU experiences, which helps them manage their feelings and issues. The nurse-led consultation may also include a visit to the ICU in specific situations: if patients have an emotional condition and express a desire to visit it. In some cases, a physician could be required to explain some medical issue that patients might have. In the nurse-led approach, the time spent with the patient might be shorter, and the costs might be lower than the consultation with a multidisciplinary team.

The evaluation by a multidisciplinary approach encompasses nurses, physicians and also physiotherapists and dieticians [5, 9, 10]. This approach characterizes a simultaneous contribution and input to the patients' issues. A whole person rehabilitation befalls via team decision maker. Although the patients' evaluation is complete at one

Table 23.1 Description of possible models of ICU follow-up clinics

Models of ICU follow-up clinics	
Led style	Nurse Physician Multidisciplinary team
Objectives	Epidemiological analysis Diagnosis and referral Treatment and rehabilitation
Timing of consultations	1 month 2 months 3 months 6 months 9 months 12 months 24 months
Interventions	Self-rehabilitation Nurse counselling Personalized care plan Specialized rehabilitation
Outcomes	Improve quality of life Decrease PICSs Decrease hospital's readmission Decrease social's costs

consultation, the financial and personnel resources needed are higher to assure the service's completion. Both situations have pros and cons; health managers choose the most appropriate option.

23.2.2 Objectives

The aims of an ICU follow-up yield benefits for patients, health workers, family members and quality of care. However, its objectives can focus on collection of data for epidemiological analysis, referral of patients to specialized professionals and rehabilitation of patients. These goals are not mutually exclusive.

An ICU follow-up starts by collecting data, which are based on tests and scores, to evaluate patients' emotional, functional and cognitive status. This produces understanding about what happens with the patients after ICU discharge and what their health requirements are. The data collection provides an easy, simple and inexpensive arrangement. Moreover, encouraging the healthcare workers to acknowledge patients' reality through the collected data might raise the awareness of long-term outcomes and their implications. Despite that, from a patient perspective, collecting data does not improve their lives or solve their impairments.

When an organized follow-up, with data collection, is running adequately, the team targets new goals such as refer and rehabilitate patients. Some studies demonstrate an

increase in adherence for patients to the ICU follow-up when the programme refers them to specialized healthcare providers such as psychiatrist and physiotherapist [11]. This approach of referral also creates a favourable opinion for patients about the ICU follow-up consultation [12].

23.2.3 The Timing of Consultation

Due to the absence of a precise timing framework for consultations after the ICU discharge, each ICU follow-up clinic chooses their plan based on guidelines, consensus and local practice. A guideline compiles instructions to develop a health programme. For ICU follow-up, the National Institute for Health and Care Excellence (NICE) has constituted guidance called "Rehabilitation after critical illness in adults" published in March 2009 [13]. It recommends that ICU survivors should be followed at 2–3 months and up to 6 months after ICU discharge. However, some studies indicate that physical recovery continues for more than 12 months after ICU admission [14–16], and other shows that cognitive impairments and mood disorders are still prevalent 5 years after ICU discharge [17].

Other ways of addressing the right timing of consultation regard extrapolating the strategy of other diseases' management which also requires a follow-up of the patient. On the one hand, Cameron et al. have adopted the timing framework from a stroke model which uses the phase-specific approach to determinate the right timing of interventions [18]. On the other hand, some ICU centres follow the ICU survivors' disabilities by endorsing the timing established by an international consensus of randomized controlled trials' outcomes – mortality – at 3–6 months.

The frequency of consultations is also controversial. The most accomplished periods are 2, 3, 6 and 12 months, whereby services that already make the programme a long time influence the organizations of others [5–7, 19–21]. Figure 23.3 demonstrates

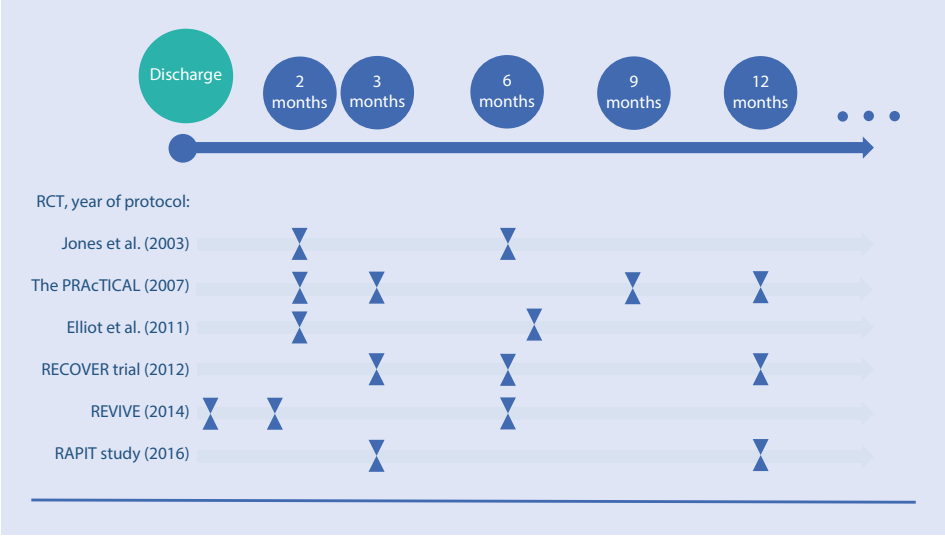


Fig. 23.3 The timing of consultations in randomized controlled trials (RCT). (Refs. [5–7, 19–21])

randomized controlled trials' protocols and their timing of intervention, showing the variance of timing framework adopted.

Moreover, looking at patients' perceptions about ICU follow-up, Farley et al. conducted a small sample ($n = 26$) study which showed 21/26 (81%) of patients stated that an ICU follow-up clinic would have been beneficial [14]. Other studies have demonstrated that the outpatients want to clarify doubts about their conditions as soon as possible, maybe weeks up to 1 month after hospital discharge rather than 3 months [12, 22]. Some patients have reported their view concerning the frequency of consultations as well. For patients who recovered well, one ICU follow-up appointment could be enough [14]. Short follow-ups are doable from a management point of view because they reduce the chance of patient loss and costs. Even though a defined benefit has not been described yet to encourage the ICU follow-up in practice, patients believe that these services are valuables [12, 23].

23.2.4 Interventions

Over the first year after ICU stay, patients confront their lives with cognitive, physical and mental impairments. Furthermore, they face difficulties to be independent and return to work. Talking about ways of addressing intervention, we have some steps to consider as screening, enrolling and evaluation during the consultation.

Definition criteria for screening patients have not been established yet. A subgroup of patients that might have benefits with the follow-up programme intervention must be described. Studies recruit patients who have had risk factors in the ICU stay to develop post-intensive care syndrome (such as delirium, sedation, prolonged stay and mechanic ventilation) [1]. However, some authors have been conducting research enrolling survivor patients at hospital discharge, using the exclusion criteria such as mechanical ventilation under 48 hours, support withdrawal and neurological sequelae [5, 19, 20].

In the UK, some services have published results about their rehabilitation strategy addressed to ICU survivors [9, 19, 24]. Even those services vary the way of delivering rehabilitation. Some of them apply a self-directed manual which illustrates how to manage the patient problems and how to perform their physical rehabilitation by themselves. Those manuals emerged from the epidemiological data acquired during the first years of follow-up consultations [19]. On the other hand, few centres use trained physiotherapists to deliver physical activities. The advantage of professional support enhances patients' confidence in themselves [20]. Some centres have also focused on active rehabilitation during ward hospitalization, improving their frequency and intensity with supervision [9]. Although all the strategies increase patients' rehabilitation, none has shown cost-effectiveness.

23.2.5 Outcomes

Several tools to access the impairments and quality of life in ICU outpatients are available (Table 23.2). Although common scales facilitate the comparison between clinical groups in research, it is not what we see represented in studies. Some follow-up services use local questionnaires, while others use standard questionnaires and validated scales to measure depression, anxiety, memory and physical disability [5, 14, 21].

Table 23.2 Summary of applicable tests to assess post-ICU impairments

Mental health	Cognitive	Physical
Hospital Anxiety and Depression Scale (HADS)	Confusion Assessment Method for the ICU (CAM-ICU)	Medical Research Council Score (MRC)
Beck Depression Inventory (BDI)	Intensive Care Delirium Screening Checklist (ICDSC)	Handgrip
Impact of Event Scale (IES)	Montreal Cognitive Assessment (MoCA)	Muscle US
Impact of Event Scale – Revised (IES-R)	Mini mental score (MMS)	Sit-to-stand test
PTSS-10	ICU-memory tool	Up-and-go test
PTSS-14		6-minute run test
Kessler Psychological Distress Scale (K10)		
36-Item Short Form Survey (SF-36)		

Moreover, an evaluation of the quality of life after discharge elucidates how interventions, which save lives, might compromise the routine of our patients in long term. Health-related quality of life (HRQoL) needs a generic instrument that encompasses different life's sectors. For ICU population, Chrispin et al. have well validated the questionnaire 36-Item Short Form Survey (SF-36) [3, 25]. Other often questionnaire applied for ICU survivors is the EuroQol-5D (EQ-5D). More information about quality of life in ▶ Chap. 12 and long-term consequences in ▶ Chap. 14

23.3 Implementation Issues in ICU Follow-up

Despite inspiring arguments to implement the ICU follow-up programme, few centres run these consultations. A national survey from the UK accomplished in 2006 demonstrated 30% of ICUs run an ICU follow-up programme [26]. The implementation of a programme confronts restrictions which interfere with its success and its benefits. One of the limitations is the lack of studies that show the benefit of follow-up implementation [3, 8, 9, 27, 28]. Hence, raising funds and financial support to design and construct this programme can be tough. The lack of data based on evidence also compromises people's engagement. The improvement of patient-centred outcomes, quality of care and satisfaction of the staff encourage people to keep their actions. All health practitioners work to enhance functional outcomes for patients. Each service designs the model that best fits within its reality, turning challenging to prove general benefit and to compare data and interventions.

Even though a few studies have demonstrated improvement in the quality of life (QoL) after ICU discharge [3, 7], the QoL does not return to the level experienced before the

illness that prompted admission. The HRQoL of ICU survivors has been reported lower compared with people who were not admitted to ICU [7, 29]. When comparing the quality of life between patients from ICU follow-up and patients with standard care, no analysis has indicated benefits yet [3]. Griffiths et al. performed a multicentre study to which observed health-related quality of life after critical illness in general ICU survivors at 6 and 12 months after ICU discharge. Their results demonstrated the median scores for QoL using the EQ-5D as 64 (interquartile range 46–80) at 6 months and 66 (interquartile range 44–80) at 12 months ($p = 0.10$) [30].

The organization of ICU team to participate in the follow-up also contributes to restriction. Due to meagre financial resources, services reorganize work schedules to allocate the same ICU team to the follow-up. Thus, this extra activity requires an already complete team, which is often not the reality. Many services have gaps in their scales and, consequently, work overload. In this context, removing a nurse to take care of an outpatient clinic rather than attending to the acute patient, which is the goal of the ICU, is a constraint.

In addition, the health system influences the progress and flow of a new programme. When the health system understands the importance of innovation and improvement, it stimulates the action of new programmes and sustains politically and financially new ideas. However, when a health system deals with lacking financial resources and high mortality rate due to sanitary reasons, for instance, the system prioritizes the reduction of the mortality rate and does not focus on patients' quality of life and their social integration after a disease. After all, patients must be alive to integrate the society.

Culture and the social context interfere with the health organization. Another barrier to the ICU outpatient clinic is the interpretation and acceptance of other health providers. Patients who are already accompanied by a specialized service such as pulmonology for chronic obstructive pulmonary disease (COPD) or cardiology for postoperative revascularization, for example, may not want to be seen by one more physician. Moreover, the intensivists should avoid being misunderstood by other specialists. The intensivist's consultation aggregate information that may be valid in the course of patients' recovery. The intensivist knows what happened in the ICU and will look at the consequences of prolonged hospitalization, mechanical ventilation or sedation. The cultural context, as well as the physicians' training, predisposes the way of thinking and judging colleagues. Correct disclosure between academic, scientific and population community reinforces the objective and safety that no one has an interest in changing or overlapping treatments. The intent is not to treat COPD or high blood pressure.

About 30% of ICU patients decline their participation in the ICU follow-up programme during enrolling stage [11, 31, 32]. In a study published in 2011 describing a follow-up programme in Sweden, Schandl et al. showed that 34% of patients rejected the invitation to participate in the programme [11]. Looking into the reasons, the most reported were patients were already accompanied by another specialty; patients did not have interest in remembering or reliving the experience of the ICU; and patients had mobility difficult for the accomplishment of the consultations.

The recovery of these patients needs a multi-specialist team. However, the level of knowledge about long-term outcomes among professionals remains short. A survey conducted in an ICU in Belgium to assess awareness showed 78% of health workers have never heard about PICS [33]. Often only journals of critical care publish papers that

address long-term outcomes after ICU discharge, which hinders general practitioners or other specialists to access and gather the information in their routine. Maybe, by publishing in general medical journals, this knowledge can be spread to reach as many number of intensivist readers as possible, improving knowledge.

The overlapping of activities – when patients take already part of another rehabilitation programme – generates a bias for data analysis. The patients' quality of life is better because of either the ICU follow-up procedures or the activities organized by other specializations.

23.4 How to Organize an ICU Follow-Up Programme

How can we perform an outpatient clinic in an efficient manner that will benefit the patient? As already mentioned, we do not have a standard template to follow so far. Some models are suggested by guidelines; others are extrapolated from other well-established programmes such as stroke and cancer. Others are merely an attempt to adapt the goodwill of healthcare providers to the reality in which they work.

We can learn from other disease's models, exploring them further by extrapolating the conditions to the ICU survivors [34]. As our training as intensivists is geared towards acute illness, we often find it difficult to understand and visualize care longitudinally. However, when we speak of PICS, even though it is not a chronic disease defined by the WHO, patients are exposed to somewhat chronic symptoms, which require prolonged care. Since survivors of the acute insult have three times more likely to die in the first year after ICU discharge and two times more likely to die within the next 15 years, we can easily understand that the syndrome has direct and indirect costs to patients and society. We should consider it for a disease management programme [35]. Likewise, we can rely on elements already described for chronic diseases, such as diabetes, to develop an appropriate model for the ICU survivor, who is a chronic patient.

Chronic care models list essential elements to ensure high-quality care longitudinally and to obtain results such as reduction of mortality [36, 37]. The disease management focuses on reduce readmissions as well as visits to the emergency room. Some of the elements covered in these models are interesting to follow. The care centre of the patients and their family and self-management support are excellent elements to guide the design of the programme, as they focus on the needs of the patients and family as well as attempting to improve patients' satisfaction and resolve their complaints. Self-management allows caregiving to be performed by the patients, that is, they are responsible for their care, including them as an actor in the scene of illness and recovery, and not reinforcing passive behaviour while waiting for treatment.

Conclusion

An ICU follow-up is a challenge for intensivists. Even though no positive impact on health-related quality of life has been demonstrated for patients yet, the ICU team intuitively think that some benefit might occur. The sense of social responsibility guides healthcare providers. A consultation after ICU discharge increases the quality of care and improves feedback to staff. The design of follow-up should be rebuilt by sharing with all levels of care in the health system this responsibility of dealing with outcomes.

Take Home Messages

- There is no standard ICU follow-up clinic
- Even though no benefit has been proven yet, patients refer interest to be followed by ICU team
- Further studies with another approach should be done to try gathering some evidence
- We should re-think our actions and goals as an ICU team

References

1. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit. Crit Care Med. 2012;40:502–9.
2. Stollings JL, Caylor MM. Postintensive care syndrome and the role of a follow-up clinic. Am J Health Syst Pharm. 2015;72(15):1315–23.
3. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med [Internet]. 2015;41(5):763–75. https://doi.org/10.1007/s00134-015-3689-1.
4. Schofield-Robinson OJ, Lewis SR, Smith AF, Mcpeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. Cochrane Database Syst Rev. 2017;2017(6).
5. Walsh TS, Salisbury LG, Boyd J, Ramsay P, Merriweather J, Huby G, et al. A randomised controlled trial evaluating a rehabilitation complex intervention for patients following intensive care discharge: the RECOVER study. BMJ Open. 2012;2(4):1–9.
6. Jensen JF, Egerod I, Bestle MH, Christensen DF, Elklit A, Hansen RL, et al. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. Intensive Care Med. 2016;42(11):1733–43.
7. Cuthbertson BH, Rattray J, Johnston M, Wildsmith JA, Wilson E, Hernendez R, et al. A pragmatic randomised, controlled trial of intensive care follow up programmes in improving longer-term outcomes from critical illness. The PRACTICAL study. BMC Health Serv Res. 2007;7:1–6.
8. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
9. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10.
10. Lasiter S, Oles SK, Mundell J, London S, Khan B. Critical care follow-up clinics. Clin Nurse Spec [Internet]. 2016;30(4):227–37. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002800-201607000-00011
11. Schandl AR, Brattström OR, Svensson-Raskh A, Hellgren EM, Falkenhav MD, Sackey PV. Screening and treatment of problems after intensive care: a descriptive study of multidisciplinary follow-up. Intensive Crit Care Nurs [Internet]. 2011;27(2):94–101. https://doi.org/10.1016/j.iccn.2011.01.006.
12. Prinjha S, Field K, Rowan K. What patients think about ICU follow-up services: a qualitative study. Crit Care. 2009;13(2):1–10.
13. Ramsay P, Salisbury LG, Merriweather JL, Huby G, Rattray JE, Hull AM, et al. A rehabilitation intervention to promote physical recovery following intensive care: a detailed description of construct development, rationale and content together with proposed taxonomy to capture processes in a randomised controlled trial. Trials. 2014;15(1):38.
14. Farley KJ, Eastwood GM, Bellomo R. A feasibility study of functional status and follow-up clinic preferences of patients at high risk of post intensive care syndrome. Anaesth Intensive Care. 2016;44(3):413–9.
15. Herridge M, Cameron JI. Disability after critical illness. N Engl J Med [Internet]. 2013;369(14):1367–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24088098

16. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up; 2013. p. 1–12. Available from: http://ccforum.com/content/17/4/R156
17. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725–38.
18. Cameron JI, Gignac MAM. "Timing it right": a conceptual framework for addressing the support needs of family caregivers to stroke survivors from the hospital to the home. Patient Educ Couns. 2008;70(3):305–14.
19. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31(10):2456–61.
20. O'Neill B, McDowell K, Bradley J, Blackwood B, Mullan B, Lavery G, et al. Effectiveness of a programme of exercise on physical function in survivors of critical illness following discharge from the ICU: study protocol for a randomised controlled trial (REVIVE). Trials. 2014;15(1):1–8.
21. Elliott D, McKinley S, Alison J, Aitken LM, King M, Leslie GD, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. Crit Care. 2011;15(3):1–10.
22. Ferguson K, Bradley JM, McAuley DF, Blackwood B, O'Neill B. Patients' perceptions of an exercise program delivered following discharge from hospital after critical illness (the revive trial). J Intensive Care Med [Internet]. 2017:88506661772473. https://doi.org/10.1177/0885066617724738.
23. Pattison NA, Dolan S, Townsend P, Townsend R. After critical care: a study to explore patients' experiences of a follow-up service. J Clin Nurs. 2007;16(11):2122–31.
24. Jones C, Eddleston J, McCairn A, Dowling S, McWilliams D, Coughlan E, et al. Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomized controlled trial. J Crit Care. 2015;30(5):901–7.
25. Chrispin PS, Scotton H, Rogers J, Lloyd DRS. Short form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. Anaesthesia. 1997;52:15–23.
26. Griffiths JA, Barber VS, Cuthbertson BH, Young JD. A national survey of intensive care follow-up clinics. Anaesthesia. 2006;61(10):950–5.
27. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. Crit Care [Internet]. 2010;14(1):R6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20089197%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2875518.
28. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev [Internet]. 2015;(6). N.PAG-N.PAG. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=109840246&site=ehost-live.
29. Hernández RA, Jenkinson D, Vale L, Cuthbertson BH. Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICaL trial. Eur J Health Econ. 2014;15(3):243–52.
30. Griffiths J, Hatch RA, Bishop J, Morgan K, Jenkinson C, Cuthbertson BH, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care [Internet]. 2013;17(3):R100. Available from: http://ccforum.com/content/17/3/R100.
31. Williams TA, Leslie GD. Challenges and possible solutions for long-term follow-up of patients surviving critical illness. Aust Crit Care. 2011;24(3):175–85.
32. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med. 2016;194(7):831–44.
33. Prevedello D, Devroey M, Yves M, Preiser J-C. Current knowledge of the ICU healthcare providers on the post-intensive care syndrome. Ann Intensive Care. 2018;8(Suppl 1):F–27.
34. Kahn JM, Angus DC. Health policy and future planning for survivors of critical illness. Curr Opin Crit Care. 2007;13(5):514–8.
35. Ellrodt G, Cook DJ, Lee J, Michaela C, Hunt D, Weingarten S. Disease management. Pdf. JAMA Intern Med. 1997;278:1687–92.

36. Grover A, Joshi A. An overview of chronic disease models: a systematic literature review. Glob J Health Sci [Internet]. 2014;7(2):210–27. Available from: http://www.ccsenet.org/journal/index.php/gjhs/article/view/41681.
37. Fireman B, Bartlett J, Selby J. Can disease management reduce health care costs by improving quality? Health Aff. 2004;23(6):63–75.

Coordinating Rehabilitation in Hospital after ICU Discharge: Priorities and Pitfalls

David M. Griffith, Judith L. Merriweather, and Timothy S. Walsh

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_24

Learning Objectives

ICU discharge is a care transition at a critical time in the patient recovery pathway. At ICU discharge, individual patient needs are high, but patients (and their families) are typically discharged to a variety of wards in the acute hospital, under multiple clinical teams, who have substantially less knowledge of their ICU-related problems and needs than the discharging ICU team.

This chapter aims to identify the key areas of unmet need for ICU survivors at transfer to the ward. We review the current limited evidence for different interventions and approaches to provide rehabilitation at this stage. Finally, we describe the principles of novel individualised service models that may improve the patient experience of recovery and potentially improve rehabilitation outcomes.

24.1 Introduction

In most healthcare systems, patients are discharged from the ICU to a hospital ward. At the time of ICU discharge, patients are frequently weak, have acutely reduced mobility, and are unable to carry out usual activities of daily living. Altered and reduced appetite is common, which compromises nutritional intake. In addition, patients face coming to terms with experiencing a life-threatening illness and its consequences. Cognitive impairments, affecting short-term memory and concentration, are likely. Many patients will have experienced delirium and may continue to do so after discharge. Recalling frightening and possible delusional memories of ICU are prevalent, as are recollections of pain and helplessness. Most patients will have ongoing sleep disturbance.

The early period of survivorship has been described by patients as a period of being 'in limbo' between their previous life and health state and the prospect of a 'new' life post-critical illness [1]. At this time, patients need and seek information about 'what has happened' and 'what to expect' going forward [1]. The contrast between the 'safety' of the ICU, characterised by high levels of care, monitoring, and access to highly trained staff, and the ward environment is a difficult and sometimes frightening transition for both patients and staff [2].

24.2 Models of Service to Meet Patient Need

24.2.1 Current ICU Rehabilitation Models

In most healthcare systems, the transition between the ICU and general ward may be a 'fracture point' in the patient pathway at a key time in the recovery journey, when the multiple interacting issues described above dominate the patient's health and wellbeing. The timing of ICU discharge is usually determined by resolution of organ failures, monitoring requirements, and treatment need in terms of medical and nursing support. Decisions are therefore dominated by service design and transitions rather than individual patient need. Typically, patients are discharged to 'parent specialties', becoming dispersed across the acute hospital in different specialty wards under the care of a wide range of different specialists, who take on decision-making from critical care teams. Consequences of this service design for post-ICU patients include the following:

- The potential for errors during the transition from ICU to the general ward, for example pharmacy resolution, communication regarding ongoing therapy needs, as well as end-of-life and/or anticipatory care decisions.
- A dilution of knowledge about individual patients, their condition, and their previous treatment in ICU.
- A general reduction in staff understanding of the consequences of critical illness, especially in relation to new weakness, nutritional requirements, and the psychological sequelae of an ICU admission.
- A sudden significant reduction in staff–patient ratios to care for individual patients and provide specialist review and therapy.
- The potential for complex, acutely disabled ICU survivors to 'compete' for limited ward resources (medical, nursing, and therapist time) with high throughput, less impaired patients (e.g. elective surgery).
- Inconsistent information provision for patients and their families, for example in relation to their critical illness and expectations of recovery.
- Limited access to existing rehabilitation pathways. Many ICU survivors do not fulfil criteria for disease-specific rehabilitation pathways as exist in many health-care systems, for example following stroke, cardiac surgery, myocardial infarction, or cancer. In addition, many ICU survivors will not fulfil criteria for rehabilitation pathways such as those specifically for older patients.

24.2.2 Key Components of Person-Centred Rehabilitation Models Following ICU Discharge

Critical illness is characterised by complexity and variability in terms of patient demographics, preexisting health, the precipitating disease process, the resulting critical illness, and the overall effects of these factors on individuals at the time of ICU discharge. Survivors therefore require an individualised approach that can promote and maximise recovery.

Some key features of individualised person-centred ward-based rehabilitation are as follows.

24.2.2.1 Physical Therapy Programmes

Critical care survivors experience a wide range of physical disability. A systematic assessment should include the following:

- Consideration of mobility and other impairments that pre-dated hospitalisation, for example related to chronic disease.
- Physical impairments that result directly from the precipitating injury, for example trauma.
- Weakness and impairments that result from critical illness neuromyopathy.

The ability to participate in physical therapy will depend heavily on symptom burden, which is frequently high following ICU discharge. Prevalent symptoms include fatigue, pain (of varying severity and distribution, but frequently involving joint stiffness), and breathlessness [3].

24.2.2.2 Nutritional Rehabilitation Programmes

Loss of appetite, altered taste, impaired gut motility and absorption, and sleep/diurnal pattern disturbance all mean most ICU survivors are unlikely to meet nutritional requirements with traditional meal service delivery. There is often a desire to remove feeding tubes on general wards, which is compounded by lack of support at mealtimes, especially for patients too weak to feed themselves. Many ICU survivors experience ongoing or worsening protein-calorie malnutrition after leaving the ICU. Approaches to address this are considered below.

24.2.2.3 Access to Occupational (OT) and Speech/Language Therapy (SLT)

The physical sequelae of critical illness frequently require support and potentially adaptations to enable activities of daily living. Early assessment by occupational therapists can anticipate likely needs and potentially facilitate earlier hospital discharge. For example, home assessments and planning for adaptations during ward-based rehabilitation can prevent delays and decrease the risk of readmission to hospital. The timing of occupational therapy requires individualised assessment by clinicians with expertise in the likely rate and degree of recovery in the ward-based period.

Similarly, patients with swallowing difficulty (especially following prolonged endotracheal intubation and/or tracheostomy) may require new or ongoing assessment and treatment from Speech and Language Therapists (SLT) to maximise oral nutrition, inform the timing of feeding tube removal, and minimise aspiration risk. Voice changes are also prevalent, and failure to recover requires referral and access to specialist assessment.

24.2.2.4 Information Provision

Qualitative research with ICU survivors in the early post-ICU period has demonstrated a need for information [1, 4]. As this coincides with the time that patients transition to the care of individuals with less specialist knowledge and understanding of critical illness, this frequently creates an unmet need among survivors and their families. The specialists taking on responsibility for ward-based care may lack the perspective required by survivors, which may include a need to 'fill in gaps' from the time in ICU, explanation of some of the physical, psychological, and cognitive sequelae (especially dealing with memories and flashbacks), and likely rates and extent of recovery.

Information can potentially be provided in various forms, including the following:

- Individual patient diaries [5]
- Generic information websites (for example, see: ► http://www.criticalcarerecovery.com/)
- Individual patient lay summaries [6]
- Visits to the ICU
- Access to trained staff to provide face-to-face information, explanation, and reassurance

The most effective way to provide individualised and generic information to patients and families is still uncertain.

24.2.2.5 Case Management and Patient Advocacy

The complexity of early ICU survivorship and rehabilitation mean continuity and consistency are key to person-centred recovery within the ward-based period of acute hospital care. This is especially evident from the traditional service-based transitions that most patients experience after leaving the ICU, in which they potentially are cared for by multiple different staff members with limited knowledge of their illness and requirements. Models in which continuity is provided, with expert case management, have been shown to be effective in other complex patient groups [7]. There is strong rationale, supported by experiential research with patients, for a case management approach to providing ward care for the ICU survivor. At a time when ICU survivors are experiencing significant physical, cognitive, and psychological disability, this approach can ensure patient advocacy. This is frequently lacking as a result of the limited recognition of ICU survivorship and the 'post-intensive care syndrome' within health care, in marked contrast to more disease or disorder-based conditions such as cancer.

24.3 Evidence for Ward-Based Rehabilitation Post ICU Discharge

24.3.1 Physical Interventions

Several randomized clinical trials have tested the effects of physical interventions delivered on the ward after ICU discharge on the physical outcomes of patients. Those that tested entirely ward-based interventions have not yet shown any benefit [8, 9]. Other trials have tested interventions initiated during ICU and continued in the ward after ICU, and these trials have been more promising. These trials are summarised in ◘ Table 24.1.

Jones and colleagues observed small improvements in the physical aspects of quality of life in patients provided with a post-ICU self-help manual, starting from ICU discharge [15]. The earliest ward-based physical rehabilitation trial was by Porta and colleagues, testing the effects of daily arm exercise training in addition to standard ward-based physiotherapy on measures of arm power and endurance [10]. The 32 patients in the intervention group demonstrated significantly greater arm power and endurance than the 34 patients in the control group. Although the study did not test the functional benefits of their intervention, and follow-up was limited to hospital discharge, the results did suggest the potential for ward-based treatments to improve strength and hence physical function. The intervention in this trial started within the ICU, but after liberation from mechanical ventilation (MV), and is probably the only trial that has demonstrated benefit to patients during the recovery phase after critical illness.

In their early (within 3 days of initiation of ventilation) mobilisation and exercise therapy trial, Scheickert and colleagues observed increased rates of functional independence in their intervention group [11]. The importance of the ward-based component could not be assessed, but many of the independence milestones were reached while patients were in ICU suggesting much of the benefit had already occurred ICU discharge.

Salisbury and colleagues published a pilot trial, which combined ward-based dietetic and physical exercise interventions delivered by a generic healthcare assistant. This showed the feasibility of the approach, which was subsequently tested in the RECOVER

Table 24.1 Summary of randomized clinical trials testing ward-based physical rehabilitation interventions

Author	Patients	Intervention	Control	Setting	Physical Outcome(s)	Conclusions
Porta (2005) [10]	66 respiratory ICU survivors (weaned from MV[a] or NIV[a] for 48–96 hours)	Daily arm cycling on arm ergometer in addition to routine care	Routine care	After weaning from MV[a] (ICU and ward)	Max arm power, endurance, and inspiratory pressure after 15 days of intervention	Arm cycling improved arm power, endurance, and maximum inspiratory pressure
Schweickert (2009) [11]	104 mechanically ventilated ICU patients	Daily progressive exercise and mobilisation protocol	Routine care	Within 72 hours of initiation of MV until hospital discharge or return to independence	Functional independence at hospital discharge, BI, number of independent ADLs, independent walking distance, HGS	Higher proportion returned to independence in intervention group
Salisbury (2010) [8]	16 mixed ICU survivors (MV[a] >48 hours)	Enhanced rehabilitation package in addition to routine care	Routine care	ICU discharge to hospital discharge	RMI[a], TUG[a], 10MWT[a], ISWT[a], HGS[a] at 3 months	No effect on physical outcomes
Walsh (2015) [12]	240 mixed ICU survivors (ventilated >48 hours)	Enhanced rehabilitation package in addition to routine care	Routine care	ICU discharge to hospital discharge	RMI[a], TUG[a], HGS[a], SF-12v2[a], PCS[a] of SF-12v2[a] at 3 months	No effect on physical outcomes
Morris (2016) [13]	300 medical ICU patients with respiratory failure receiving ventilation (MV[a] via ETT[a] or NIV[a])	Protocolised physical therapy intervention	Routine care	ICU admission to hospital discharge	SPPB[a], SF-36[a], PCS[a] and PFS[a] of SF-36[a], FPI[a], HGS[a] at 2, 4, and 6 months	Inconsistent effect on outcomes: improved SPPB at 2 months, SF-36[a] PFS[a] and PCS[a] at 6 months, and FPI[a] at 6 months

Table 24.1 (continued)

Author	Patients	Intervention	Control	Setting	Physical Outcome(s)	Conclusions
Gruther (2017) [14]	60 ICU patients (>5 day stay, rehabilitation ready)	Breathing, mobilisation exercises, and NMES[a]	Routine care	From ICU discharge to hospital discharge	ERBI[a], 3MWT[a], MRC[a] sum score	No effect on physical outcomes

[a]*Abbreviations*: *MV* mechanical ventilation, *NIV* non-invasive ventilation, *ADL a*ctivity of daily living, *BI* Barthel Index, *RMI* Rivermead mobility index, *TUG* timed up and go test, *HGS* hand grip strength, *10MWT* 10 minute walk test, *ISWT* incremental shuttle walk test, *SF-36* Medical Outcomes Study short form 36, *PCS* physical component score, *PFS* physical function score, *SF12 v2* Medical Outcomes Study short form 12 version 2, *FPI* functional performance inventory, *NMES* neuromuscular electrical stimulation, *ERBI* early rehabilitation Barthel Index, *3MWT* 3 minute walk test, *MRC* Medical Research Council

randomised controlled trial in 240 ICU survivors [8]. RECOVER showed that individualised case management could increase ward-based physical therapy, but the intervention showed no effect on mobility, HRQOL, hand grip strength, or the timed up and go test at any follow-up time points. Patients reported greater satisfaction with the therapies they received, including the coordination of care and information provided [9].

In trial of 300 patients with respiratory failure, Morris and colleagues added a standardised thrice daily exercise therapy programme to standard care for ICU patients [13]. Like the RECOVER intervention, patients received a ward-based intervention until hospital discharge. Unlike RECOVER, treatment was initiated on ICU admission (RECOVER recruited an ICU survivor cohort). Morris demonstrated no effect on hospital length of stay (the primary outcome), ventilator free days, or ICU days. At 2 and 4 months, measures of physical function (short physical performance battery, SF-36 PFS and PCS, and FPI score) were unchanged, but small differences in these scales were detected at 6 months.

Finally, Gruther and colleagues' 60-patient trial testing the addition of a ward-based rehabilitation to standardised ICU-based rehabilitation for long-term ICU patients found no improvement in their primary outcome (the number of days between ICU and hospital discharge) or a number of other secondary outcomes.

In summary, current evidence demonstrates no clear physical benefits from ward-based post-ICU interventions, most of whom progress to experience long-term physical weakness [16].

24.3.2 Nutritional Therapy

24.3.2.1 Nutritional Status of Critical Illness Survivors

Malnutrition is prevalent among critically ill patients and, in one study, was found in 43% of general ICU admissions [17]. Malnutrition is associated with longer hospital stay and complications compared to previously well-nourished individuals. During ICU

admission, patients can lose 10–30% of their body mass [18]. Compounding this weight loss is suboptimal nutritional intake in the ICU, with patients typically receiving only 60–80% of their prescribed energy and protein requirements [19]. This results from delays in initiating nutritional support [20] and reduced nutritional intake due to vomiting, large gastric aspirates, enteral feeding tube displacement, and fasting for investigations and procedures.

The nutritional status of patients frequently deteriorates further during the ward phase of care [21]. A study on 50 patients for 7 days post-extubation found only one patient consumed greater than 75% of their calorie requirements on day 1 post-extubation, with mean energy and protein intake less than 50% of estimated requirements on all 7 days of the study period [22]. Similarly, Merriweather [23] and Rowles et al. [24] found oral intake to be inadequate in the post-ICU phase. Failure to meet nutritional requirements is likely to have a negative impact on muscle mass and physical or functional ability [25]. For the post-ICU patient, good nutritional care is fundamental to the recovery process.

24.3.2.2 Factors Influencing Nutritional Recovery in ICU Survivors

Despite extensive nutrition-related research in ICU, little is known about nutritional recovery in patients after critical illness. Peterson et al. found poor appetite and nausea were barriers to eating [22]. In a qualitative study, multiple factors were identified that contributed to patients' failure to achieve nutritional goals [26, 27]. Analysis of sequential interviews and observations revealed a number of themes including nutritional care delivery failures such as the inflexibility of hospital meals, failure to deliver nutritional supplements, and lack of staff knowledge about critical illness-related issues. Patient-related factors that emerged included physiological and psychosocial issues such as poor appetite, early satiety, taste changes, low mood, and depression. Patients also experienced social isolation and struggled with lack of familiar food and routine. The identified factors that influence nutritional recovery interlink serving to increase the complexity of nutritional problems for this patient group.

The process of nutritional recovery has multiple linked elements including appetite, physical ability to eat, personal preferences, and emotional influences. Superimposed on these are the systems that deliver nutrition to patients. If all these form links in a chain that lead to nutritional recovery, it is entirely possible that a single break in the chain could disrupt the benefits from all the other elements. Hence, there is a need to understand as many components of recovery in order to develop the best complex intervention [23].

24.3.2.3 Nutritional Rehabilitation Strategies in Post-ICU Phase of Care

There is remarkably little nutrition-specific research concerning post-ICU rehabilitation. The National Institute of Clinical Excellence failed to identify any studies that specifically addressed nutritional rehabilitation in patients after critical illness [28].

Work with ICU survivors suggests that improvements in nutritional rehabilitation require an individualised model of care to address the identified organisational and patient-related factors that influence nutritional recovery [23]. This approach challenges

Table 24.2 Comparison of traditional approach to nutritional care with proposed model of care

Traditional approach to nutritional care of post-ICU patients	Proposed approach to nutritional care of post-ICU patients
Fragmented care means ward staff including nurses and doctors are often unaware of problems experienced by patients after critical illness. Patients often isolated inside rooms eating alone in bed. Lack of assistance at mealtimes to patients who are often weak and fatigued. Restricted family presence during food service time. Systems-based approach to delivery of food with set mealtimes three times a day. Standard portion sizes with a starter, main meal, and pudding all served at once. Patients experience physiological and psychological problems after critical illness that are not addressed. Dietetic interventions involving the calculation of nutritional requirements and comparing to actual nutritional intake; documentation of recommendations in medical notes; ordering of nutritional supplements with a reliance of other healthcare professionals to deliver poorly coordinated discharge and nutritional follow-up.	A clearly documented nutritional management plan should be handed over to ward staff and appropriate allied health professionals to ensure continuity of nutritional care. Providing patient with the opportunity to eat with family members either on ward or in the canteen. Involvement of relatives at mealtimes on the ward to provide assistance, encouragement, and social interaction. Improving problems with poor appetite and early satiety by providing small regular energy-dense meals and snacks. Information given to patient about importance of nutrition for recovery and the need to eat foods high in calories and protein to achieve this. Regular feedback to the patient as to whether they are achieving their nutritional goals. Recognising psychological issues associated with critical illness and discussing common problems with patient and if necessary referring to appropriate healthcare professional. Assisting the patient to come to terms with changes to their body, setting patient-centred goals for recovery. Early reporting of ongoing nutritional problems to appropriate healthcare staff. Identification of discrepancies in nutritional decision-making, for example between medical and dietetic staff. Coordination of discharge to ensure patient has all relevant nutritional information and follow-up in the community.

the traditional approach to nutritional care and requires service redesign to address the multiple potential barriers to nutritional recovery (Table 24.2).

Merriweather identified the need to address nutritional issues during different phases of the patients' hospital journey [23]. The three distinct phases of care were prior to transfer from ICU, during ward stay, and on discharge from hospital. A patient pathway was devised to define the key elements of nutritional care for post-ICU patients during each of the stages of care (Table 24.3).

Table 24.3 Proposed care pathway for the nutritional care of ICU survivors

Prior to discharge from the Intensive Care Unit	
Goal 1: The patient's nutritional issues are identified early	☐ Preexisting malnutrition prior to ICU admission (BMI < 18 kgm^2, history of weight loss and/or history of poor nutritional intake) ☐ Long ICU stay (>7 days) ☐ Swallowing problems Patient experiencing physiological factors influencing nutritional intake. ☐ Loss of appetite ☐ Early satiety ☐ Taste changes ☐ Pain ☐ Nausea/vomiting ☐ Diarrhoea ☐ Fatigue ☐ Breathlessness ☐ Changes to sleep patterns Patient experiencing psychological factors influencing nutritional intake ☐ Delirium ☐ Low mood ☐ Cognitive changes ☐ Depression
Goal 2: The patient's identified nutritional issues are communicated to ward staff	Handover to ward staff to include: ☐ Current route for nutrition ☐ Identified factors influencing nutritional intake ☐ Nutritional plan
During ward stay	
Goal 3: The patient is receiving the appropriate amount and type of nutrition	☐ Weekly weight ☐ Review by dietitian ☐ Referral to speech and language therapy (if necessary) ☐ Food record charts
Goal 4: The patient's ongoing physiological issues are identified	☐ Loss of appetite ☐ Early satiety ☐ Taste changes ☐ Pain ☐ Nausea/vomiting ☐ Diarrhoea ☐ Fatigue ☐ Breathlessness ☐ Changes to sleep patterns Issues are discussed with multidisciplinary team

Table 24.3 (continued)

Prior to discharge from the Intensive Care Unit	
Goal 5: The patient's ongoing psychological issues are identified	☐ Delirium ☐ Low mood ☐ Cognitive changes ☐ Depression Issues are discussed with multidisciplinary team
Goal 6: The patient has the appropriate provision of food	☐ Meals served one course at a time ☐ Meals provided at suitable times ☐ Family encouraged to bring in favourite foods ☐ Provision of meals from canteen where necessary ☐ Additional snacks are provided between meals ☐ Assistance with eating is provided where necessary ☐ Eating with others is encouraged
Goal 7: The patient is aware of the importance of good nutrition	☐ Emphasising the need to eat more for physical recovery ☐ Discussion of factors affecting nutritional intake ☐ Regular feedback to patient about adequacy of oral intake ☐ Involvement of family in discussions
Goal 8: The patient's nutritional needs are discussed regularly by the multidisciplinary team (MDT)	☐ Weekly multidisciplinary meetings ☐ Dietitian highlights any nutritional issues ☐ The need for nutritional support is reviewed by the MDT
On discharge from hospital	
Goal 9 The patient is provided with appropriate nutritional information	☐ Written dietary information ☐ Supply of nutritional supplements ☐ Contact details ☐ Regular follow-up

24.4 Guidance and Quality Standards for Post-ICU Ward-Based Rehabilitation

The paucity of studies to support strategies and effective components of ward-based rehabilitation mean guidance lacks a firm base. The UK National Institute of Clinical Excellence (NICE) makes a number of recommendations regarding rehabilitation prior to ICU discharge and during ward-based care [28]. These highlight the need for individualised screening and assessment (Table 24.4).

Table 24.4 Summary of NICE recommendations for post-ICU rehabilitation [28]

Recommendations Prior to Ward Discharge	*Before discharge from critical care* For patients who were previously identified as being at low risk, perform a short clinical assessment before their discharge from critical care to determine their risk of developing physical and non-physical morbidity. For patients at risk and patients who started an individualised, structured rehabilitation programme in critical care perform a comprehensive clinical reassessment to identify their current rehabilitation needs. The comprehensive reassessment should pay particular attention to: Physical, sensory, and communication problems Underlying factors, such as preexisting psychological or psychiatric distress Symptoms that have developed during the critical care stay, such as delusions, intrusive memories, anxiety, panic episodes, nightmares, flashback episodes, or depression. For patients who were previously identified as being at risk during critical care, the outcomes of a comprehensive reassessment should inform the individualised, structured rehabilitation programme For patients at risk, agree or review and update the rehabilitation goals, based on the comprehensive reassessment. The family and/or carer should also be involved, unless the patient disagrees. Ensure that the transfer of patients and a formal structured handover of their care occur. This should include a formal handover of the individualised, structured rehabilitation programme. Give patients the following information before, or as soon as possible after, their discharge from critical care. Also give the information to their family and/or carer, unless the patient disagrees. Information about their rehabilitation care pathway. Information about the differences between critical care and ward-based care. This should include information about the differences in the environment and staffing and monitoring levels. Information about the transfer of clinical responsibility to a different medical team If applicable, emphasise the information about possible short-term and/or long-term physical and non-physical problems that may require rehabilitation. If applicable, information about sleeping problems, nightmares, and hallucinations and the readjustment to ward-based care
Recommendations for ward-based rehabilitation	For patients who were previously identified as being at low risk before discharge from critical care, perform a short clinical assessment to determine their risk of physical and non-physical morbidity. For patients at risk, perform a comprehensive clinical reassessment to identify their current rehabilitation needs. For patients at risk, offer an individualised, structured rehabilitation programme, based on the comprehensive clinical reassessment and the agreed or updated rehabilitation goals set before the patient was discharged from critical care. The individualised, structured rehabilitation programme should be developed and delivered by members of a multidisciplinary team and should include appropriate referrals, if applicable. Based on clinical judgement and the individual patient's rehabilitation needs, consider offering a structured and supported self-directed rehabilitation manual for at least 6 weeks after discharge from critical care, as part of the individualised, structured rehabilitation programme. For patients with symptoms of stress related to traumatic incidents and/or memories, refer to 'post-traumatic stress disorder (PTSD)' guidance, and initiate appropriate preventative strategies

Case Study: The Edinburgh Generic Rehabilitation Assistant (GRA) Model

As part of a programme of research and service development work in Edinburgh, Scotland, we systematically identified unmet needs among ICU survivors during the first 2–3 months following discharge from the ICU, including the ward-based post-ICU period. We developed a novel multidisciplinary therapist role, a Generic Rehabilitation Assistant (GRA), to provide additional therapy for ICU survivors in conjunction with the established ward-based team [29]. The GRA received competency-based training in physical therapy (PT), dietetics, SLT, OT, and psychological support relevant to patients discharged from the ICU. These individuals, and the therapies they delivered, were evaluated in a randomised parallel group trial (RECOVER) that compared usual care in two UK National Health Service hospitals with care supplemented by the GRA between ICU discharge and up to 3 months post-randomisation.

The RECOVER trial demonstrated that increased frequency and intensity of all elements of rehabilitation, including comprehensive information provision to patients and families, could be delivered with this service model in an efficient and coordinated manner. There was discordance between the effects the intervention had on clinical outcomes at 3–12 months post-ICU discharge and the satisfaction patients had with their rehabilitation together with their experience of recovery. The trial showed no impact on measures of physical function, psychological status, patient-reported symptoms, or quality of life. However, subsequent secondary analyses have shown that pre-illness health status dominates these outcomes post critical illness, which may limit their responsiveness and validity as outcomes in rehabilitation trials [30]. In contrast, patients reported improved satisfaction and a better experience of their early recovery using questionnaire and qualitative methodologies [12, 31].

Key benefits of the GRA role were providing a patient-centred approach to care, enabling individualised therapy, ensuring consistency, and continuity of care. A key benefit perceived by patients is as an advocate or ambassador for the patient as they traverse service transitions under the care of multiple different clinicians. The GRA also makes a major contribution to hospital discharge planning and the transition to community living.

Take Home Messages

- ICU survivors have diverse physical, psychological, cognitive, and information needs when discharged to the general ward
- The transition to ward-based care can result in substantial unmet need as a result of reduced staff knowledge of post-ICU complications and reduced staffing intensity.
- There are currently no evidence-based strategies or interventions that improve clinical outcomes in this period.
- Approaches that meet individual patient needs across the range of potential issues can improve patients' experience and satisfaction with rehabilitation.
- Key areas to address are:
  - Physical and functional limitations
  - The multiple patient- and system-based barriers to nutritional rehabilitation
  - Patients and families' need for information
  - Patient advocacy and consistency of care

References

1. Kean S, Salisbury LG, Rattray J, Walsh TS, Huby G, Ramsay P. "Intensive care unit survivorship" – a constructivist grounded theory of surviving critical illness. J Clin Nurs. 2017;26(19–20):3111–24. https://doi.org/10.1111/jocn.13659.
2. Field K, Prinjha S, Rowan K. "One patient amongst many": a qualitative analysis of intensive care unit patients' experiences of transferring to the general ward. Crit Care. 2008;12(1):R21. https://doi.org/10.1186/cc6795.
3. Griffith DM, Salisbury L, Lee RJ, Lone N, Merriweather JL, Walsh T. The burden of specific symptoms reported by survivors after critical illness. Am J Respir Crit Care Med. 2017;197(2):269–72. https://doi.org/10.1164/rccm.201702-0398LE.
4. Deacon KS. Re-building life after ICU: a qualitative study of the patients' perspective. Intensive Crit Care Nurs. 2012;28(2):114–22. https://doi.org/10.1016/j.iccn.2011.11.008.
5. Ullman AJ, Aitken LM, Rattray J, et al. Diaries for recovery from critical illness. Cochrane Database Syst Rev. 2014;12:CD010468. https://doi.org/10.1002/14651858.CD010468.pub2.
6. Ramsay P, Huby G, Merriweather J, et al. Patient and carer experience of hospital-based rehabilitation from intensive care to hospital discharge: mixed methods process evaluation of the RECOVER randomised clinical trial. BMJ Open. 2016;6(8):e012041. https://doi.org/10.1136/bmjopen-2016-012041.
7. Ham C, Imison C, Jennings M. Avoiding hospital admissions: lessons from evidence and experience – Ham, Imison, Jennings – the king's fund, October 2010. 2010. www.kingsfund.org.uk. Accessed 29 Apr 2018.
8. Salisbury L, Merriweather J, Walsh T. The development and feasibility of a ward-based physiotherapy and nutritional rehabilitation package for people experiencing critical illness. Clin Rehabil. 2010;24(6):489–500. https://doi.org/10.1177/0269215509360639.
9. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge. JAMA Intern Med. 2015;175(6):901. https://doi.org/10.1001/jamainternmed.2015.0822.
10. Porta R, Vitacca M, Gilè LS, et al. Supported arm training in patients recently weaned from mechanical ventilation. Chest. 2005;128(4):2511–20. https://doi.org/10.1378/chest.128.4.2511.
11. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82. https://doi.org/10.1016/S0140-6736(09)60658-9.
12. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10. https://doi.org/10.1001/jamainternmed.2015.0822.
13. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure. JAMA. 2016;315(24):2694. https://doi.org/10.1001/jama.2016.7201.
14. Gruther W, Pieber K, Steiner I, Hein C, Hiesmayr JM, Paternostro-Sluga T. Can early rehabilitation on the general ward after an intensive care unit stay reduce hospital length of stay in survivors of critical illness?: a randomized controlled trial. Am J Phys Med Rehabil. 2017;96(9):607–15. https://doi.org/10.1097/PHM.0000000000000718.
15. Jones C, Eddleston J, McCairn A, et al. Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomized controlled trial. J Crit Care. 2015;30(5):901–7. https://doi.org/10.1016/j.jcrc.2015.05.002.
16. Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane collaboration systematic review. J Cachexia Sarcopenia Muscle. 2016;7(5):520–6. https://doi.org/10.1002/jcsm.12146.
17. Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. Nutrition. 1996;12(1):23–9. http://www.ncbi.nlm.nih.gov/pubmed/8838832. Accessed April 20, 2018
18. Griffiths RD, Jones C. Recovery from intensive care. BMJ. 1999;319(7207):427–9.. http://www.ncbi.nlm.nih.gov/pubmed/10445926. Accessed April 20, 2018
19. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. Crit Care Med. 2010;38(2):395–401. https://doi.org/10.1097/CCM.0b013e3181c0263d.

20. Wandrag L, Gordon F, O'Flynn J, Siddiqui B, Hickson M. Identifying the factors that influence energy deficit in the adult intensive care unit: a mixed linear model analysis. J Hum Nutr Diet. 2011;24(3):215–22. https://doi.org/10.1111/j.1365-277X.2010.01147.x.
21. Nematy M, O'Flynn JE, Wandrag L, et al. Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study. Crit Care. 2006;10(1):R10. https://doi.org/10.1186/cc3957.
22. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. J Am Diet Assoc. 2010;110(3):427–33. https://doi.org/10.1016/j.jada.2009.11.020.
23. Merriweather JL, Lorna J. Exploration of the factors that influence nutritional recovery following critical illness: a mixed methods study. July 2014. https://www.era.lib.ed.ac.uk/handle/1842/9571. Accessed 20 Apr 2018.
24. Rowles A, Langan A, Bear DE. SUN-P019: oral intake and appetite in the intensive care unit. Clin Nutr. 2016;35(Suppl 1):S51. https://doi.org/10.1016/S0261-5614(16)30362-4.
25. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017;21(1):226. https://doi.org/10.1186/s13054-017-1810-2.
26. Merriweather J, Smith P, Walsh T. Nutritional rehabilitation after ICU – does it happen: a qualitative interview and observational study. J Clin Nurs. 2014;23(5–6):654–62. https://doi.org/10.1111/jocn.12241.
27. Merriweather JL, Salisbury LG, Walsh TS, Smith P. Nutritional care after critical illness: a qualitative study of patients' experiences. J Hum Nutr Diet. 2016;29(2):127–36. https://doi.org/10.1111/jhn.12287.
28. Rehabilitation after critical illness in adults|Guidance and guidelines|NICE. https://www.nice.org.uk/guidance/qs158/chapter/Quality-statement-1-Rehabilitation-goals. Accessed 20 Apr 2018.
29. Salisbury LG, Merriweather JL, Walsh TS. Rehabilitation after critical illness: could a ward-based generic rehabilitation assistant promote recovery? Nurs Crit Care. 2010;15(2):57–65. https://doi.org/10.1111/j.1478-5153.2010.00382.x.
30. Griffith DM, Salisbury LG, Lee RJ, Lone N, Merriweather JL, Walsh TS. Determinants of health-related quality of life after ICU. Crit Care Med. 2018;46(4):594–601. https://doi.org/10.1097/CCM.0000000000002952.
31. Walsh TS, Salisbury LG, Boyd J, et al. A randomised controlled trial evaluating a rehabilitation complex intervention for patients following intensive care discharge: the RECOVER study. BMJ Open. 2012;2(4):e001475. https://doi.org/10.1136/bmjopen-2012-001475.

Cost of Disability

David Orlikowski

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_25

Learning Objectives

To know what are the main outcomes of postintensive care syndrome in terms of utilization of care and induced cost after ICU stay both in the hospital and after discharge. To know what are the impact and burden on caregivers, ability to work, and income reduction for ICU survivors.

25.1 Introduction

25

Utilization of critical care has grown over the past two decades, with improvement of quality of care that change prognosis and mortality, creating a growing number of ICU survivors [1].

Admission to ICU is a potent marker of acquired multimorbidities and medical complexity. Outcome studies in ICU survivors have emphasized severe physical and cognitive decline and the development of mood disorders [2]. This morbidity is a direct consequence of our ability to save the lives of our most severely ill patients and the addition of complicated multimorbidities and chronic multisystem dysfunction. The resulting disabilities are associated with compromised long-term survival, more hospital and ICU readmissions, specialist use, and high costs [3].

For example, in USA between 17.4% and 39.0% of total hospital costs are spent for critical care with a cost for treating ICU patients between 121 and 263 billion dollars [4].

Societal burden could also be very important for patient by impacting ability to work and diminishing their income dramatically [5] (Table 25.1).

Table 25.1 Principal complications induced by ICU from Desai et al. [1]

Complication	Description	Natural history
Pulmonary	Spirometry impairment, lung volume, and diffusion	Improves generally during first year but may persist up to 5 years
Neuromuscular	Critical illness neuropathy and myopathy	Polyneuropathy recovers slowly than myopathy and extends to 5 years
Physical function	Impairment in activities and instrumental activities in daily living Impairment in 6-minute walk test	Improvement within months, at 1 year for daily activities and 2 years for instrumental activities.
Psychiatric symptoms	Depression Posttraumatic stress disorder Anxiety	May decrease over first year Little improvement in first year May persist after first year
Cognitive	Impairment in memory, attention and executive function	May improve during the first year
Quality of life	Deficits essentially on quality physical domains	Improve over first year, could persist during 5 years

25.2 Postintensive Care Syndrome

25.2.1 Definition

The term "postintensive care syndrome" (PICS) was agreed on as the recommended term to describe new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute-care hospitalization. The term could be applied to a survivor (PICS) or family member (PICS-F) [6].

A subgroup of these patients are qualified of chronically critically ill patients. These patients often needed prolonged ventilation [3] and have a poor outcome include poor quality of life, high mortality, high readmission rate, high rehabilitation needs, and generate a high cost of cares [7].

25.2.2 The Different Complications Post ICU

Except mortality that ranges from 26% to 63% after 1 year and a risk of death up to 5 times more in the long-term than age-matched control several complications can be observed in the long term after critical care [1].

These complications can impact pulmonary, neuromuscular, physical psychiatric, cognitive functions, and quality of life [1].

25.2.3 Pulmonary Function

Long-term pulmonary function was essentially studied in patients with Acute Respiratory Distress Syndrome. A variable range of impairments were observed: restrictive, obstructive, and reduced diffusion capacity. Persisting use of ventilation or oxygen therapy is relatively rare [8]. Spirometry and lung volume impairments improved usually quickly within months rather than diffusion capacity abnormalities, which are related to invasive ventilation duration than can take among 5 years to recover [9, 10].

Prolonged duration of mechanical ventilation is usually observed in aged patients more than 60 years old that have multiple comorbidities. Between 30% and 53% of chronically critically ill patients are liberated form mechanical ventilation during ICU stay [11, 12].

25.2.4 Neuromuscular Function

Nearly 50% of patients with sepsis, multiorgan failure, or prolonged mechanical ventilation are suffering from critical illness neuromyopathy, a term including both critical illness myopathy and neuropathy. These complications are associated with an increased ICU, hospital stay, and require prolonged rehabilitation use [13].

25.2.5 Physical Function

Physical function is usually assessed by measuring both patient's (walking, dressing, eating, etc.) and instrumental (e.g., shopping, managing money, or preparing a meal) activi-

ties of daily living (ADL) and 6-minutes walking test (6 MWT). Physical function impairment was found in all patients discharged from ICU at 1 week but may persist in more than 50% of survivors for patient's ADL after 1 year with severe impairment in one-third of patients [14, 15]. Instrumental ADL stays impaired in more than 70% of survivors that were ventilated more than 48 h mainly related to age and preexisting activities.

25.2.6 Psychiatric Disorders

The psychiatric complications after ICU occur frequently, with symptoms of depression and anxiety (including posttraumatic stress disorders PTSD). Depressive symptoms have an estimated prevalence around 30% in several studies [16, 17]. This is a markedly higher prevalence than general population evaluated around 8%.

For PTSD and anxiety after ICU, the median estimated prevalence were 22% and 24%, respectively. In contrast to PTSD when compared to the general population, the prevalence is 3.5% [18].

Duration of such troubles is unclear but seems to decrease after the first year for depressive symptoms [19] and persists many years after for PTSD [16].

25.2.7 Cognitive Disorders

Cognitive impairment including delirium is a very common feature observed during ICU stay. Delirium is mainly related to overuse of sedation and correlated to an higher mortality. In another study on acohort of aged Americans, severe sepsis was associated to a tripling of the odds of moderate/severe cognitive impairment [20]. Persisting cognitive sequelae are variable in 46–71% of patients at 1 year [21, 22].

25.2.8 Quality-of-Life Impairment

Quality of life is commonly impaired after ICU discharge and is potentially for a long duration.

Impairments in ICU survivors concern mostly the domains related to physical quality of life.

Several factors have been associated with quality-of-life impairment including preexisting disease, severity of illness during ICU stay, depression, and posttraumatic stress disorder.

Physical domain deficits are associated with critical illnesses such as neuropathy, muscle mass wasting, and impaired pulmonary function.

25.2.9 Impact and Burden on Caregivers

An high family and caregiver burden is observed whatever of condition of the patient illness critical or chronic. This may induce high rates of depression and decline of physical health. The need of prolonged ventilation and tracheotomy placement being a major component of this burden.

Year male gender and tracheostomy at 12 months were the main factors associated to caregivers depression symptoms, and lifestyle disruption [23].

In another study longitudinal study, depression risk, lifestyle disruption, and employment reduction were commonly observed in caregivers and persisted over 1 year, similar to risks observed in Alzheimer disease and chronic illnesses.

Most of caregivers were women aged more than 50 years old and spend nearly 6 hours/day providing assistance [24]. The dependency status before ICU admission had no influence on caregiver's burden.

25.2.10 Induced Cost After ICU

About 40% of patients are required to continue medical care for 2 years after initial hospitalization [9].

The majority of these costs are related to rehabilitation, hospital readmission, age, and organ dysfunction. For example, for ARDS patients, 40% are readmitted to hospital and half of them are admitted for multiples times [8].

The costs linked to ICU cares are the most important around 100,000 dollars per patient followed by cost related to wards, and post-discharge cost around 30,000 dollars at 2 years (mostly nursing care at home and rehabilitation use).

At discharge 33% of patients need inpatient rehabilitation and more than a half of discharged patients at home need home care services in the 2 following years after ICU admission, [9]. Physical therapy and psychiatric visits were the most costly outpatient categories: 46% of ARDS survivors required physical therapist and 19% occupational therapist [8], while 18% visited a psychiatrist and 48% of survivors used psychiatric medications

25.2.11 Job and Lost Earnings

In a 2 years study on ARDS survivors, 49% at 1 year and 65% of survivors returned to job at 1 and 2 years, respectively [9] mostly to their preceding jobs.

On a 5-years period, the proportion of patients ever returned to job was 51% at 1 year, 45% at 2 years, and only 31% at 5 years of employed ARDS survivors ever returned to job [25]. Time to return to work was associated with a high Charlson comorbidity index, mechanical ventilation duration, and discharge to an healthcare facility after ICU [25]. In another study from the same team, 49% of previously employed survivors from ARDS were jobless at 6 months and 44% at 1 year. Half of them who returned to work, returned by 13 weeks after hospital discharge and 68% at 1 year. The inability to return to work was linked to age (patients aged more than 48 years old) and the nonwhite race status (32% at 1 year versus 64%) [5].

Forty three percent never returned to their previous work, 27% reported reduced effectiveness at work, and 31% experienced a major occupation change with reduction of worked hours time.

The cumulative lost earning after ARDS was estimated at around 180,000 U.S. dollars over a 5-year period. Limitation of working due to disability accounted for 55% of cumulative lost earnings [25]. Over 12-month follow-up, nonretired survivors accrued an average lost earning of 27,000 U.S. dollars, representing 60% of the pre-ARDS annual income [5].

A decrease in coverage of private insurance and an increase of government-funded healthcare coverage were reported between 14–33% and 16–37%, respectively [9].

Conclusion

Postintensive care syndrome is commonly observed in survivors of ICU patients. It associates a lot of physical, cognitive, psychological, and societal complications. This is also associated to a high consumption of care and therefore high induced costs during hospital stay and after hospital discharge. Persisting needs for ventilation and tracheostomy seem to be the principal factors of burden. The impact is not limited to patients but concern caregivers and family. Economical consequences include employment reduction and loss of earning up to 60% of the pre-ICU admission annual income.

Take Home Messages

- Postintensive care induces high morbidity and high related costs during ICU stay but also after discharge.
- The need for home care service, need for physical rehabilitation, as well as psychological and psychiatric cares are the most common features after ICU discharge
- The impacts on ability to work and incomes lowering are important. They induce occupational changes and a mean lost of earning around 30,000 a year.
- The main responsible factors are the level of disability and the persisting need of mechanical ventilation

References

1. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med. 2011;39(2):371–9. PubMed PMID: 20959786.
2. Azoulay E, Vincent JL, Angus DC, Arabi YM, Brochard L, Brett SJ, et al. Recovery after critical illness: putting the puzzle together-a consensus of 29. Crit Care. 2017;21(1):296. PubMed PMID: 29208005. Pubmed Central PMCID: 5718148.
3. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182(4):446–54. PubMed PMID: 20448093. Pubmed Central PMCID: 2937238.
4. Coopersmith CM, Wunsch H, Fink MP, Linde-Zwirble WT, Olsen KM, Sommers MS, et al. A comparison of critical care research funding and the financial burden of critical illness in the United States. Crit Care Med. 2012;40(4):1072–9. PubMed PMID: 22202712.
5. Kamdar BB, Huang M, Dinglas VD, Colantuoni E, von Wachter TM, Hopkins RO, et al. Joblessness and Lost Earnings after Acute Respiratory Distress Syndrome in a 1-Year National Multicenter Study. Am J Respir Crit Care Med. 2017;196(8):1012–20. PubMed PMID: 28448162. Pubmed Central PMCID: 5649982.
6. Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, et al. Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit Care Med. 2014;42(12):2518–26. PubMed PMID: 25083984.
7. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. Am J Crit Care. 2007;16(5):447–57. PubMed PMID: 17724242. Pubmed Central PMCID: 2040111.
8. Ruhl AP, Huang M, Colantuoni E, Karmarkar T, Dinglas VD, Hopkins RO, et al. Healthcare utilization and costs in ARDS survivors: a 1-year longitudinal national US multicenter study. Intens Care Med. 2017;43(7):980–91. PubMed PMID: 28550403.

9. Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006;174(5):538–44. PubMed PMID: 16763220.
10. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med. 2016;194(7):831–44. PubMed PMID: 26974173.
11. Engoren M, Arslanian-Engoren C, Fenn-Buderer N. Hospital and long-term outcome after tracheostomy for respiratory failure. Chest. 2004;125(1):220–7. PubMed PMID: 14718444.
12. Carson SS, Garrett J, Hanson LC, Lanier J, Govert J, Brake MC, et al. A prognostic model for one-year mortality in patients requiring prolonged mechanical ventilation. Crit Care Med. 2008;36(7):2061–9. PubMed PMID: 18552692. Pubmed Central PMCID: 2728216.
13. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. JAMA. 1995;274(15):1221–5. PubMed PMID: 7563512.
14. Chaboyer W, Elliott D. Health-related quality of life of ICU survivors: review of the literature. Intensive Crit Care Nurs. 2000;16(2):88–97. PubMed PMID: 11868593.
15. van der Schaaf M, Dettling DS, Beelen A, Lucas C, Dongelmans DA, Nollet F. Poor functional status immediately after discharge from an intensive care unit. Disabil Rehabil. 2008;30(23):1812–8. PubMed PMID: 19031208.
16. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosom Med. 2008;70(4):512–9. PubMed PMID: 18434495.
17. Davydow DS, Zatzick DF, Rivara FP, Jurkovich GJ, Wang J, Roy-Byrne PP, et al. Predictors of posttraumatic stress disorder and return to usual major activity in traumatically injured intensive care unit survivors. Gen Hosp Psychiatry. 2009;31(5):428–35. PubMed PMID: 19703636. Pubmed Central PMCID: 2732585.
18. Kessler RC, Avenevoli S, Costello J, Green JG, Gruber MJ, McLaughlin KA, et al. Severity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry. 2012;69(4):381–9. PubMed PMID: 22474106. Pubmed Central PMCID: 3522117.
19. Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JF Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. Gen Hosp Psychiatry. 2010;32(2):147–55. PubMed PMID: 20302988.
20. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787–94. PubMed PMID: 20978258. Pubmed Central PMCID: 3345288.
21. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340–7. PubMed PMID: 15542793.
22. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513–20. PubMed PMID: 20473145. Pubmed Central PMCID: 3638813.
23. Van Pelt DC, Schulz R, Chelluri L, Pinsky MR. Patient-specific, time-varying predictors of post-ICU informal caregiver burden: the caregiver outcomes after ICU discharge project. Chest. 2010;137(1):88–94. PubMed PMID: 19762552. Pubmed Central PMCID: 2803119.
24. Van Pelt DC, Milbrandt EB, Qin L, Weissfeld LA, Rotondi AJ, Schulz R, et al. Informal caregiver burden among survivors of prolonged mechanical ventilation. Am J Respir Crit Care Med. 2007;175(2):167–73. PubMed PMID: 17068327. Pubmed Central PMCID: 1899280.
25. Kamdar BB, Sepulveda KA, Chong A, Lord RK, Dinglas VD, Mendez-Tellez PA, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. Thorax. 2018;73(2):125–33. PubMed PMID: 28918401.

Cost-Effectiveness of Postintensive Care Clinics

X. Willaert, Bharath Kumar Tirupakuzhi Vijayaraghavan, and B. H. Cuthbertson

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_26

Learning Objectives

In this chapter, we provide the reader with insights into the clinical outcomes and financial aspects of post-ICU clinics. In the first part of the chapter, we start by defining the costs of a post-ICU clinic and provide an overview of methods commonly used to assess the effectiveness of healthcare interventions, such as post-ICU clinics. A framework will also be provided to combine and integrate both cost and effectiveness assessment of these clinics. In the second part of the chapter, we discuss the two landmark trials on cost-effectiveness of post-ICU clinics to conclude that they are not cost-effective due to a lack of evidence for their effectiveness. Finally, we will conclude the chapter by proposing some ideas for future research.

26

26.1 Introduction

It is estimated that at least half of ICU survivors suffer from Postintensive Care Syndrome (PICS), which is characterized by a new or worsening decline in physical, cognitive, and/or mental health [1–3]. Given the high prevalence and complexity of the syndrome, healthcare interventions to improve the quality and duration of life after ICU are likely to require a multidisciplinary approach.

The cost of modern healthcare interventions may outweigh the economic benefits in healthcare systems particularly in those that are already under financial pressure. Policy makers require tools to allocate the available resources responsibly and according to societal needs and willingness to pay. One of the methods available to policy makers is cost-effectiveness analysis (CEA) in which the net costs of an intervention will be related to the expected benefits. In this chapter, we will outline the essentials of CEA and apply it to interventions for postintensive care syndrome.

26.2 Cost, Effectiveness, and Cost-Effectiveness Analysis

26.2.1 Defining Cost

Providing intensive care services is an expensive healthcare intervention, and survivors of intensive care have a continued need for ongoing care after ICU and hospital discharge. Although data on postintensive care expenditure is scarce and literature reports on different aspects of care are available, a recent systematic review by Lone and colleagues highlights some key elements [4]. During the first year after discharge from hospital, expenditure peaks with an estimated cost ranging from US $18,847 to US $148,454. More than half of these costs arise from acute care with a lesser contribution from care provided by community healthcare workers. Given the high costs of ongoing secondary care and hospital readmissions [5], a pre-emptive strategy using postintensive care clinics to avoid readmission is a candidate intervention to attempt to reduce healthcare costs. The effectiveness of postintensive care clinics has not yet been demonstrated; however, given the complexity of PICS, a clinic will likely require a multidisciplinary team. Based on the experience of UK- and US-based clinics, these clinics are typically staffed by a critical care physician, pharmacist, psychologist/psychiatrist, nurse, dietician, occupational therapist, and physiotherapist [6, 7]. Architectonic requirements for a clinic may not only include consultation offices, but also a rehabilitation unit and gym. Prior to making calculations

regarding the costs of a proposed clinic, we need to properly understand how to define costs in healthcare.

Defining cost as the net expenditure requires not only a clear delineation of the different types of costs, but also a scope on the timeframe of the expenditure and to whose budget the expenditure is attributed. In general, costs in medicine can be subdivided into two main categories: cost of providing the health intervention and access costs [8, 9]. The costs of providing the intervention such as a postintensive care clinic can be further categorized into two different categories – fixed or variable. Fixed costs are typically independent of patient volume the intervention addresses; for example, rent of the clinical space required to host a postintensive care clinic remains fixed independent of whether we treat few or many patients per day. Variable costs on the other hand are patient volume dependent, for example, lab tests, drug prescriptions costs, etc. Typically, the fixed costs of running a clinic far outweigh the variable costs.

Costs can also be divided into direct and indirect costs. Direct costs can be directly attributed to patient care, for example, time a physiotherapist or physician spends seeing patients at the clinic. Indirect costs, often referred to as overheads, are the costs that cannot be linked to a single patient and are shared among patients, for example, electricity and heating, time staff spend writing reports, etc. Based on the composition of healthcare teams staffing such clinics, it may be clear that costs for staff will be the main expenditure. Access costs on the other hand are the costs that are made by patients and their families in order to be able to take part in healthcare delivery. Examples of access costs are transportation and lodgings. When determining costs, one must also consider the optimal time allowance for delivery of the care offered to a patient. It must be recognized that the longer we spend on any individual patient, the less likely the intervention is to be cost-effective.

From a societal perspective, there are two important cost considerations. First of all, there is the question of who pays for the clinics. If the patient or a private insurance pays for the intervention, the cost is not transferred to the public and does not include a loss of opportunity for society (at least directly). A second cost consideration is the decreased productivity and lost income by the patient and their family caregivers. A study performed by Griffiths et al reported that one-third of patients discharged from intensive care had a negative impact on employment and income at 1 year [10]. Approximately one-fifth of patients required assistance with the activities of daily living at 1 year. In the majority of cases, this help was provided by a family member, who had to make significant adjustments to their work schedules in half of the cases. In less than 10% of all cases, the supporting family member also had a significant drop in employment activity for at least 1 year. According to the results of a smaller trial performed by Quasim et al., approximately only two-thirds of patients who were working prior to ICU admission had returned to work at 2 years after discharge [11]. These factors should ideally be included in a cost-effectiveness analysis.

26.2.2 Defining Effectiveness

Since PICS is a complex syndrome spanning multiple levels of human wellbeing, it may be difficult to determine the exact impact of interventions treating PICS. The WHO definition of health as "a state of complete physical, mental and social well-being not merely in the absence of disease or infirmity" significantly overlaps with the domains affected by PICS [12]. In the medical literature, the 5 domains of health (physical, psychological,

social, economic, and religion), as defined by Spilker, are often reduced to the first 3 of these domains and are referred to as health-related quality of life (HRQoL) [13, 14]. Multiple instruments exist to measure the HRQoL; however, the SF-36 and EQ-5D or "EuroQol 5 dimensions" are well established and partially validated in the critical care literature [14]. The SF-36 consists of 36 questions spanning 8 domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Scoring of each domain will generate a score between 0 and 100 per domain, with higher scores representing better health [14, 15].

Although the SF-36 questionnaire was not designed to generate a single number representing a general state of health, an increasing amount of scientific papers report on the "SF-36 total score". Since this total score is not supported by the designers of the SF-36 and there is no accurate method of calculation, a degree of skepticism should be maintained regarding this score. Despite the fact that the 8 domains should not be combined to one number, it is possible to deduct a physical and mental score, respectively, referred to as the physical component summary (PCS) and mental component summary (MCS). Calculations incorporating weighing factors for the different domains are done by private company–owned algorithms [15]. Shorter variations of the SF-36 (e.g. SF-12) were designed to reduce survey length and patient burden.

The EQ-5D is made up by 2 components: a descriptive component and the EQ-VAS score. The descriptive component measures health in 5 dimensions: mobility, self-care, usual activities, pain, and anxiety/depression. In the descriptive component, the respondent will be asked to answer questions according to 5 levels ranging from no problems to extreme problems. The EQ-VAS records the patient's self-reported health by marking an "X" on a 20 cm vertical scale ranging from 0 to 100 with the extremes of the scale labeled as "best imaginable health state" and "worst imaginable health state" [16]. The inclusion of the EQ-VAS score into the EQ-5D has the advantage that the HRQoL obtained by the descriptive component can be weighted and valued, which is in contrast to the SF-36 that will require additional techniques such as time trade-off or standard gamble to value the health state [17]. Although both weighing techniques are fundamentally different, they both use clinical scenarios with patient preferences for specific health states to determine the HRQoL weights. In the time trade-off technique, patients are asked to choose between living a longer life with a disability state or having a shorter life in perfect health. The time period in full health is then varied until the patient is indifferent to both the choices. The standard gamble confronts the patients with a choice between remaining in the current state of health or taking a gamble for perfect health, but risking death. The probability of risking death varies until the patient is indifferent between certainty and gamble.

Although SF-36 and EQ-5D are validated, several limitations should be considered. First of all, self-reported quality of life is often referred to as "subjective" and dependent on the feeling of well-being, which may have been reset from the patient's baseline due to a feeling of having conquered death. As such a patient may have false-positive feelings regarding his/her proficiency in the activities of daily life or regarding his/her feelings of anxiety and depression. This "cheated death" phenomenon was described earlier by Cuthbertson et al. [18] Second, HRQoL is in fact variable in time and it may be challenging to choose the best time-frame to evaluate the HRQoL after a healthcare intervention, since treatment effect may vary over time with a potential risk for over- or underestimation (mostly under). We note that the identification of HRQoL assessment as being

"subjective" is misleading. Of course, the assessment of HRQoL by a patient about their own HRQoL is subjective, but it is their subjectivity, which they are entitled to. Surely subjectivity is only a problem for outcome measurement when it is the observer who introduces it into the measurement.

Critical care survivors have ongoing physical and psychological problems affecting quality of life after discharge. Although quality of life improves within the first year, it typically does not reach the same level of quality of age- and sex-matched controls (although they were also lower before ICU admission). A cohort study performed by Cuthbertson et al. showed that physical quality-of-life scores rose to premorbid levels at 1 year, but that this improvement was reversed between 2.5 and 5 years. Interestingly, despite well-described psychological problems in this population, data show that mental quality-of-life score rapidly improved and rose back to population norm at 6 months [18].

26.2.3 Quality-Adjusted Life Years (QALY), Willingness to Pay (WTP), and Incremental Cost-Effectiveness Ratio (ICER)

Once the HRQoL weights have been calculated, QALY or quality-adjusted life years can be calculated by multiplying the HRQoL weight by the years lived in that particular health state. One year lived in perfect health equals 1 QALY, while 1 year lived in a health state with an associated HRQoL weight of 0.7 equals 0.7 QALYs. Figure 26.1 depicts a simplified theoretical model of the effects that an ICU admission and post-ICU interventions could potentially have on QALYs gained. At the time of the ICU admission, the HRQoL acutely drops (although the premorbid baseline is low compared to age- and sex-matched

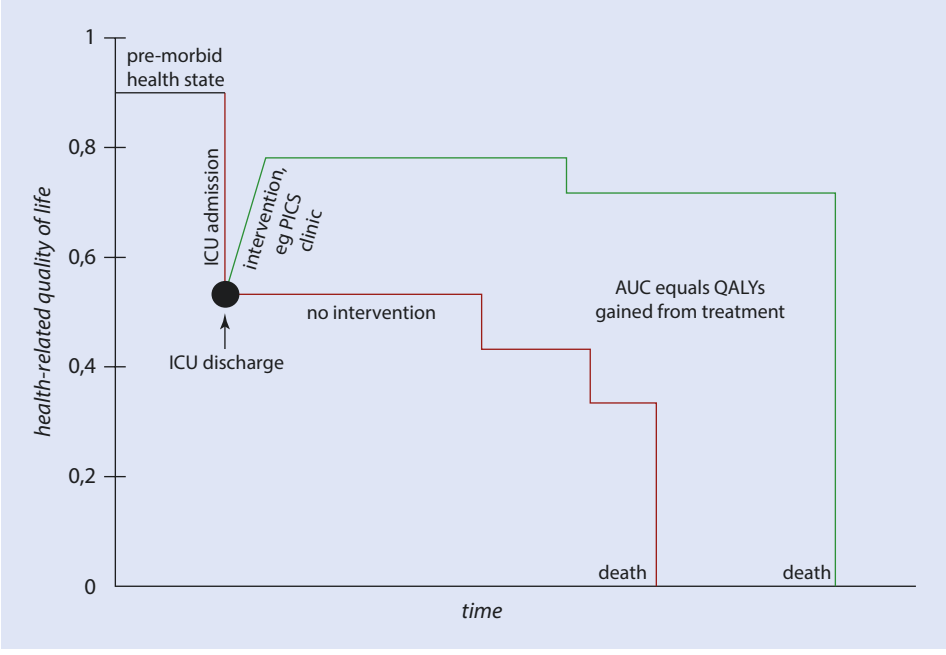


Fig. 26.1 QALY after ICU and healthcare interventions. (Adjusted from Whitehead et al. [17])

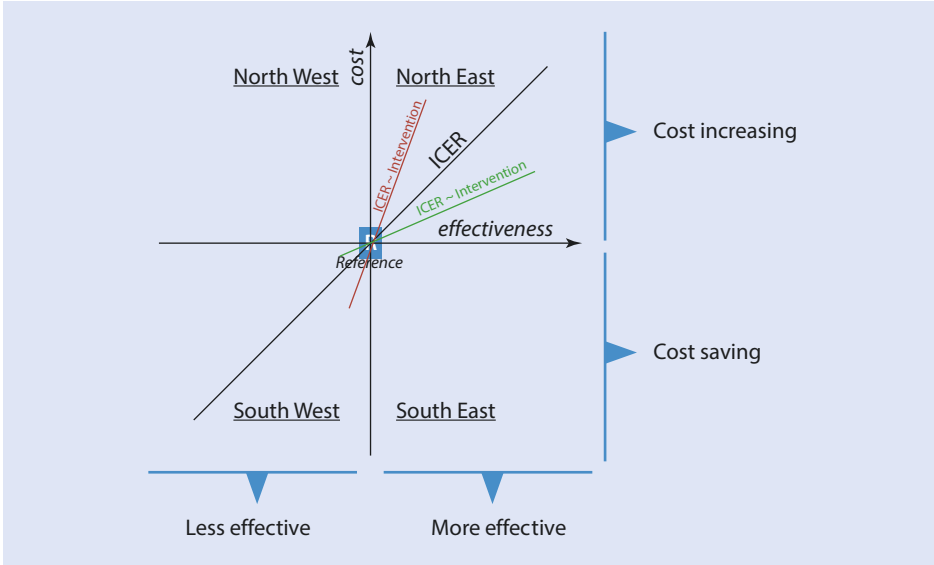


Fig. 26.2 Cost-effectiveness plane and plotted ICER. (Adjusted from Cohen et al. [19])

controls). If the patient is discharged from the ICU alive, the HRQoL is lower than the premorbid state without any interventions, the HRQoL remains low, and further decreases until the patient ultimately dies (red line). If a (theoretical) treatment is offered, the HRQoL gradually improves and the patient not only lives longer, but also gains a higher HRQoL score (green line). The area between the green and red curves equals the additional QALYs gained by the intervention.

Once the effectiveness of an intervention is established, the cost-effectiveness can be determined by linking the cost to the QALYs gained or lost. A first method to conceptualize cost-effectiveness is by plotting the data on a cost-effectiveness plane (Fig. 26.2). On this plane, the position on the x-axis depicts the effectiveness, while the position on the y-axis shows the associated cost. The intersection of both axes (named R, Reference) illustrates the reference value for an already established therapy. By plotting the data of newer therapies on the graph, a comparison to the reference will give insight in cost-effectiveness. In the best scenario, a new intervention is situated in the southeast quadrant, which indicates an increased effectiveness at reduced cost in comparison to current therapy. In the southwest quadrant, the new intervention is less costly but also less effective but could still be cost-effective. Interventions situated in the northwest quadrant should be rejected, since they combine a reduced effectiveness at increased price. The northeast quadrant corners interventions that have increased effectiveness, but come at a higher price and may be cost-effective depending on the cost. A second method to evaluate cost-effectiveness in trials is to determine the "incremental cost-effectiveness ratio" (ICER). The ICER is defined as the difference in cost between two interventions divided by the difference in QALY. It represents the incremental cost to obtain one additional QALY. The angle between the black ICER line and the x-axis will be determined by society's willingness to pay. If society is willing to pay more per QALY gained, the angle will increase and vice versa for a lower willingness to pay per QALY. The ICER of a specific intervention can be plotted on the cost-effectiveness plane by connecting data points from the intervention

to the reference data [19]. The red ICER line represents an intervention with a higher cost per QALY gained, while the green ICER line represents an intervention with a lower cost per QALY gained.

There remains the question of at what level the cost-effectiveness threshold is set at by society; in other words, what is a society willing to pay for one QALY gained? Historically, this threshold was set at US $50,000 in the mid-1990s and despite higher estimates, this cut-off is still often used in North American literature [20]. In the United Kingdom, on the other hand, this threshold was set at £20,000–£30,000, but on occasions can be higher [21]. A recent systematic review by Nimdet et al reports on society's willingness to pay (WTP) per QALY gained [22]. It appears that a dichotomy exists between the WTP for interventions that save lives and interventions that affect quality of life. Life-saving interventions were valued higher with a cost-effectiveness threshold of two times the global domestic product (GDP) per capita, while interventions improving quality of life were valued at only 0.6 times the GDP per capita. These data are in contrast with the WHO recommendations, which set the threshold at two to three times the GDP per capita per QALY gained, or approximately US $110,000 to $160,000 per QALY gained [20, 23].

26.3 Cost-Effectiveness of Postintensive Care Clinics

In the early 1990s, the awareness of "life after intensive care" significantly rose and in an attempt to improve the quality of life, the first post-ICU clinic was started in 1993 in Reading, UK [24]. In the years following, more post-ICU clinics were organized throughout the UK and also in Australia. In 2011, the first post-ICU clinic was started in the USA. Despite unproven efficacy of post-ICU clinics, their popularity and presumed need keeps growing. Before examining the cost-effectiveness of postintensive care clinics, we need to ascertain their effectiveness.

In a randomized controlled multicentre trial performed in three UK-based hospitals with well-established postintensive care clinics, routine follow-up was compared to a combination of follow-up plus a 6-week self-help rehabilitation manual [25]. The study showed a trend toward improved physical recovery at 6 months as indicated by a higher score on the "z score" of the SF-36 score for the intervention group. There was no effect on anxiety and posttraumatic stress disorder–related symptoms at 6 months. A cohort trial performed from 2006 until 2009 evaluated the effects of follow-up consultations on anxiety and depression. Patients were invited to a multidisciplinary consultation (held by nurse, physician, and physiotherapist) at 3, 6, and 12 months after ICU discharge. At the time of the consultation, patients were offered a visit to the ICU and the ICU events were explained. Patients were also screened for psychiatric and physical problems. If the team suspected any problems in mental or physical recovery, the patient was offered referral to a psychiatrist or physiotherapist respectively. Study results showed that psychological problems were more common in women than in men and that the study intervention could have a positive effect on symptoms of anxiety and depression in women [26].

Although the aforementioned trials provide some information on the effects of postintensive care clinics, they do not offer any insights in the effects on HRQoL and cost-effectiveness. The PRaCTICaL and RECOVER trial are two well-designed randomized controlled trials that studied both HRQoL and cost-effectiveness of postintensive care clinics. The PRaCTICaL trial is a multicentre trial performed in three UK-based hospitals [27]. One of the hospitals already had a postintensive care clinic (Reading) and assisted in

setting up the program in the other two hospitals. In this study, a total of 286 mechanically ventilated patients discharged from intensive care unit were included, irrespective of the length of stay, and were randomized in two study groups. The control group had standard follow-up by their general practitioner and primary hospital specialist. The intervention group received a manual based self-directed physical rehabilitation program designed by a physiotherapist. The manual was introduced in hospital by a study nurse and was to be continued until 3 months after discharge from hospital. At 3 and 9 months after hospital discharge, patients were formally reviewed at nurse-led, physician-supported clinics. During these clinic visits, patients' ICU experiences were discussed and the need for specialist medical or psychiatric referral was assessed. Patients were also offered a visit to the ICU. Assessment at 12 months showed that there was no significant difference between both groups with respect to HRQoL as measured by the SF-36 physical and mental score. The mean scores on the SF-36 physical component was 42 (SD 10.6) for the intervention group compared to 40.8 (SD 11.9) for the control group (50 being the age- and sex-matched population mean). For the SF-36 mental component, the intervention group mean score was 47.1 (SD 12.7), while the control group mean score was 46.8 (SD 12.4). Since the trial did not account for length of ICU stay, a subgroup analysis including patients with ICU stays longer than 3 days was performed; however, it did not have a significant treatment effect. In the economic evaluation, the study paired the estimated cost with the gained QALYs. Cost estimations were made per patient by linking data from questionnaires and hospital notes to study specific cost estimations and governmental-published data of healthcare costs per intervention. QALYs were calculated from the AUC derived from EQ-5D questionnaires, which were valued for a UK population. The intervention resulted in a mean total QALY gain of 0.423 at a mean cost of £7126. In comparison to the control group, where a mean cost of £4810 resulted in 0.426 QALY gain, the intervention was significantly more expensive than standard care. Despite the fact that the cost of the intervention is still below society's willingness-to-pay threshold, the intervention is simply not cost-effective, since there is no difference in QALY. In fact, this analysis suggests it would be cost-effective to withdraw ICU follow-up clinics from practice.

The RECOVER trial was conducted between 2010 and 2013 in two UK hospitals [28]. The study randomized a total of 240 patients – that had received more than 48 hours of mechanical ventilation – after discharge from the ICU. After randomization, all patients received a self-help post-ICU rehabilitation manual to guide their recovery. A ward-based multidisciplinary team consisting of physical, occupational, and speech -and-language therapists provided tailored care to all patients. In contrast to the control group, the patients in the intervention group not only received care at a higher frequency and intensity, they were also provided with information, which was thought to be helpful for their recovery. To comply with the increased workload in the intervention group, the team of therapists was supported by three multiskilled research assistants assigned solely to the patients receiving the intervention. The research assistants also coordinated the delivery of additional information by offering patients a meeting with an ICU consultant to discuss their ICU stay, by providing a lay summary of the ICU events and by offering a visit to the ICU. After hospital discharge, research assistants tried to contact patients at least once to check up on them and to provide them with contact details for support. Despite increased mobility, exercise, and occupational therapy, the results are rather disappointing. At 3, 6, and 12 month assessment, there was neither significant group difference in mobility scores, nor in HRQoL and depression/anxiety symptoms. The mean QALY, as calculated by SF-12, was 0.54 (SD 0.20) for the intervention group and 0.54 (SD 0.18) for the control group.

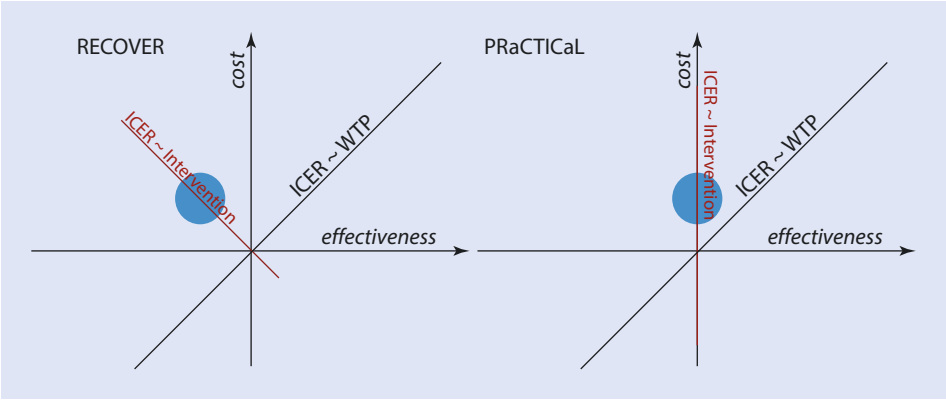


Fig. 26.3 Cost-effectiveness planes for RECOVER and PRaCTICaL trial

Due to a lack of data on primary healthcare utilization, cost estimations were limited to secondary care costs from randomization to 1-year follow-up. The mean costs for the intervention group was calculated at £49,000 (with a range from £7000 to £249,000) and was similar to the cost of the control group, which was also £49,000 (range £10,000–£304,000). To account for the wide range of secondary healthcare costs and estimations of the intervention delivery costs, a linear regression analysis was performed. The results showed that the intervention led to a nonsignificant additional cost of £2000. The RECOVER trial concluded that the intervention as such was not cost-effective.

Figure 26.3 depicts a simplified cost-effectiveness plane for both RECOVER and PRaCTICaL trial. For the RECOVER trial, results are situated in the northwest quadrant, making the intervention less effective at a higher cost. The PRaCTICaL trial shows a similar effectiveness in both groups; however, the intervention is more costly. The black ICER line represents the incremental cost society would be willing to pay per QALY gained, while the red ICER line represents the incremental cost according to the intervention.

26.4 Future Research

As illustrated by the PRaCTICaL and RECOVER trial, complex interventions for postintensive care rehabilitation provide neither clear benefit on outcome nor on cost-effectiveness. Several factors, such as residual neuromyopathy and protracted inflammatory response, may account for the lack of efficacy of physical therapy after ICU. Critical illness myopathy and polyneuropathy affect up to two-thirds of patients requiring critical care and up to one-third have residual symptoms at discharge from the hospital [29]. Persistent neuromyopathy may not only hinder physical therapy, it may also limit the inherent ability to actually recover. Furthermore, it was illustrated by the RECOVER trial group that not only the majority of patients had a proinflammatory phenotype at 3 months after discharge, but that this was also associated with poor physical recovery [30]. The exact timing and "dosage" of physical therapy is still unclear. It is even possible that classical physiotherapy may not be effective in this syndrome. Future research may need to focus on a tailored approach according to individual inflammatory biomarker levels and EMG studies to decide on the timing [30] of initiation and nature of recovery programs.

Take Home Messages

- Costs of modern healthcare interventions can outweigh the available resources and put pressure on healthcare systems. Cost-effectiveness analysis will help policy makers to allocate the resources responsibly and according to societal needs.
- An increasing awareness of the devastating consequences of PICS on the quality of life of ICU survivors has led to a move toward following up patients in post-ICU clinics. Despite the unproven efficacy of these clinics, the number of post-ICU clinics is growing.
- The PRaCTICaL and RECOVER trial studied the cost-effectiveness of post-ICU clinics and illustrated that these clinics are not cost-effective, due to a lack of effectiveness. Based on these trials, it would be cost-effective to withdraw ICU clinics from practice.

References

1. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit. Crit Care Med. 2012;40:502–9.
2. Sukantarat K, Greer S, Brett S, Williamson R. Physical and psychological sequelae of critical illness. Br J Health Psychol. 2007;12:65–74.
3. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. J Trans Int Med. 2017;5:90. https://doi.org/10.1515/jtim-2016-0016.
4. Lone NI, Seretny M, Wild SH, Rowan KM, Murray GD, Walsh TS. Surviving intensive care. Crit Care Med. 2013;41:1832–43.
5. Ruhl AP, Lord RK, Panek JA, et al. Health care resource use and costs of two-year survivors of acute lung injury. An observational cohort study. Ann Am Thorac Soc. 2015;12:392–401.
6. Huggins EL, Stollings JL, Jackson JC, Sevin CM. Models for a Post-Intensive Care Syndrome Clinic – Targeted Goals and Barriers. In: SCCM.org. http://www.sccm.org/Communications/Critical-Connections/Archives/Pages/Models-for-a-Post-Intensive-Care-Syndrome-Clinic%2D%2D-Targeted-Goals-and-Barriers.aspx. Accessed 18 Feb 2018.
7. Rehabilitation after critical illness in adults | guidance ... nice.org.uk/guidance/qs158. Accessed 18 Feb 2018.
8. Coughlin MT, Angus DC. Economic evaluation of new therapies in critical illness. Crit Care Med. 2003;31:S7. https://doi.org/10.1097/00003246-200301001-00002.
9. WHO. Making choices in health WHO guide to cost-effectiveness analysis. Geneva: World Health Organization; 2003.
10. Griffiths J, Hatch RA, Bishop J, Morgan K, Jenkinson C, Cuthbertson BH, Brett SJ. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013;17:R100. https://doi.org/10.1186/cc12745.
11. Quasim T, et al. Employment, social dependency and return to work after intensive care. J Intens Care Soc. 2015;16(1):31–6.
12. WHO (1970) The first ten years of the World Health Organization. In: apps.who.int. http://apps.who.int/iris/handle/10665/37089. Accessed 18 Feb 2018.
13. Spliker B. Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott Williams & Wilkins; 1996.
14. Wu A, Gao F. Long-term outcomes in survivors from critical illness. Anaesthesia. 2004;59:1049–52.
15. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. SAGE Open Med. 2016;4:205031211667172.
16. van Reenen M, Janssen B. EQ-5D-5L User Guide – EuroQol. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. Accessed 18 Feb 2018.

17. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5–21.
18. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010;14:R6. https://doi.org/10.1186/cc8848.
19. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. J Am Coll Cardiol. 2008;52:2119–26.
20. Neumann PJ, Cohen JT, Weinstein MC. Updating cost effectiveness – the curious resilicience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371:796. https://doi.org/10.1056/NEJMp1405158.
21. Judging whether public health interventions offer value for money. In: Guidance and guidelines | NICE. http://www.nice.org.uk/guidance/lgb10. Accessed 18 Feb 2018.
22. Nimdet K, Chaiyakunapruk N, Vichansavakul K, Ngorsuraches S. A systematic review of studies eliciting willingness-to-pay per quality-adjusted life year: does it justify CE threshold? PLoS One. 2015;10:e0122760. https://doi.org/10.1371/journal.pone.0122760.
23. WHO Macroeconomics and health. Investing in health for economic development. Report of the commision on macroeconomics and health. In: http://www1.worldbank.org/publicsector/pe/PEAMMarch2005/CMHReport.pdf. Accessed 18 Feb 2018.
24. Griffiths JA, Gager M, Waldmann C. Follow-up after intensive care. Conti Educ Anaesth Crit Care Pain. 2004;4:202–5.
25. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, Waldmann C, Gager M. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31:2456–61.
26. Schandl A, Bottai M, Hellgren E, Sundin Ö, Sackey P. Gender differences in psychological morbidity and treatment in intensive care survivors – a cohort study. Crit Care. 2012;16:R80. https://doi.org/10.1186/cc11338.
27. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
28. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge. JAMA Intern Med. 2015;175:901.
29. Hermans G, Berghe GVD. Clinical review: intensive care unit acquired weakness. Crit Care. 2015;19:274. https://doi.org/10.1186/s13054-015-0993-7.
30. Griffith DM, Lewis S, Rossi AG, Rennie J, Salisbury L, Merriweather JL, Templeton K, Walsh TS. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. Thorax. 2016;71:820–9.