David S. Warner, M.D., Editor

Acquired Muscle Weakness in the Surgical Intensive Care Unit

Nosology, Epidemiology, Diagnosis, and Prevention

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ABSTRACT

Muscle weakness is common in the surgical intensive care unit (ICU). Low muscle mass at ICU admission is a significant predictor of adverse outcomes. The consequences of ICU-acquired muscle weakness depend on the underlying mechanism. Temporary drug-induced weakness when properly managed may not affect outcome. Severe perioperative acquired weakness that is associated with adverse outcomes (prolonged mechanical ventilation, increases in ICU length of stay, and mortality) occurs with persistent (time frame: days) activation of protein degradation pathways, decreases in the drive to the skeletal muscle, and impaired muscular homeostasis. ICU-acquired muscle weakness can be prevented by early treatment of the underlying disease, goal-directed therapy, restrictive use of immobilizing medications, optimal nutrition, activating ventilatory modes, early rehabilitation, and preventive drug therapy. In this article, the authors review the nosology, epidemiology, diagnosis, and prevention of ICU-acquired weakness in surgical ICU patients. (Anesthesiology 2016; 124:207-34)

MUSCLE weakness occurs as frequently as low arterial blood pressure in the surgical intensive care unit (SICU).[1–3] The incidence of sarcopenia (low skeletal muscle mass) in the intensive care unit (ICU) can be as high as 70%,[4] depending on the age, presentation, and comorbidities of the patient, and preexsiting sarcopenia predicts adverse discharge disposition.[5] Muscle mass decreases by approximately 2% per day as a consequence of patients' acute disease and their ICU treatment.[6–9]

The current interest in surgical ICU-acquired weakness (ICUAW) is because of the associated significant and potentially long-term adverse outcomes for patients as well as the substantial costs involved in caring for this complication and its consequences. Associated adverse outcomes include joint contractures, thromboembolic disease, insulin resistance, microvascular dysfunction, pressure ulcers, respiratory complications (atelectasis, pneumonia, weaning failure), and delirium, translating into increased ICU and hospital length of stay, impaired functional status and neuropsychologic impairment that can persist for up to and over a year after surgery, increased readmission rate, and mortality.[10–20]

In this article, we review the nosology, epidemiology, diagnosis, and prevention of ICUAW in surgical ICU patients. We also highlight the potential for drug targets and gene therapy in the prevention of ICUAW.

Nosology: Classification of Diseases Related to Skeletal Muscle Weakness

Muscle weakness is difficult to reliably quantify—small differences in the clinical testing procedure lead to meaningful differences in results. In addition, ICU healthcare providers

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of different professions may have different beliefs regarding what constitutes a "weak patient," and based on the nosologic misunderstandings, their management of the weak patient can vary widely.[21] Precise use of the terminology will help better synchronize efforts of scientists, physicians, nurses, and physical therapists to eliminate ICU-acquired muscle weakness.

Sarcopenia (derived from Greek word σάρξ sarx meaning "flesh" and πενία penia meaning "poverty") is the loss of skeletal muscle mass, which can be reliably quantified by muscle ultrasound in the ICU even in unconscious patients.[5] Sarcopenia is a component of frailty, which is the status of decreased physical and cognitive reserve leading to an increased vulnerability to stressors. A diagnosis of frailty can be made by using validated instruments such as interviewing the patient regarding their baseline functional status with questions.[5] Furthermore, assessment of mobility, muscle mass, nutritional status, strength, and endurance are all valid identifiers of clinically weak patients. Dynapenia is the frailty-associated loss of muscle strength that is not caused by neurologic or muscular diseases.

Muscle strength is defined as the amount of force that a muscle, or a group of muscles, can produce to overcome resistance with a single maximal effort.[22] Several factors impact the amount of force generated, such as neural drive to the skeletal muscles, the number and size of muscle fibers, number and functionality of acetylcholine receptors, muscle length at the time of stimulation, and frequency of stimulation.[22] The ability of a muscle to overcome resistance repetitively is called endurance. The main determinants of endurance are the maximal oxygen uptake and the rate of glycogen depletion.[23] Lack of endurance promotes a reduction in the exercise-induced capacity to generate force over time,[24] which is known as muscle fatigue. Muscle fatigue can be classified, based on the evoked response to repeated muscle stimulation, into two types: (1) low-frequency fatigue (relative loss of force at low frequencies of stimulation and a slow recovery over the course of hours or even days) and (2) high-frequency fatigue (excessive loss of force at high frequencies of stimulation and rapid recovery when the frequency is reduced).[25] Fatigue and deficits in endurance impair muscle performance leading to lack of muscle strength or dynapenia.

The term ICUAW typically describes the bilateral and symmetrical neuromuscular sequelae of critical illness, which occurs during the ICU stay and not related to another specific etiology.[26] ICUAW can be recognized through clinical manifestations such as difficult weaning from mechanical ventilation, flaccid tetraparesis or tetraplegia, hyporeflexia, and muscular atrophy,[27] which affects limb, respiratory, and pharyngeal muscles.[28]

Epidemiology of Postoperative Muscle Weakness

Many patients develop transient muscle weakness after surgery as a consequence of residual neuromuscular blockade, opioid therapy, or inflammation.[29,30] The surgical site, the type of surgical technique (*e.g.*, open *vs.* laparoscopic), and the pharmacokinetics of anesthetics and neuromuscular-blocking agents (NMBAs) determine the magnitude and the duration of postoperative muscle weakness. Open abdominal and thoracic surgical interventions are associated with prolonged impairment in respiratory function and an increased risk of postoperative complications.[31] These complications can result in postoperative mechanical ventilation being required for longer than 24 h,[32,33] which further increases the risk of muscle weakness and diaphragmatic atrophy.[34] Conversely, laparoscopic surgeries are associated with a faster recovery of grip strength and inspiratory force as early as 2 to 3 h after emergence from anesthesia.[31]

Severe muscle weakness can persist for over a year after surgery.[14,35] The incidence of persistent weakness at 1 yr has been found to be around 20 to 30% for localized procedures such as modified radical mastectomy[14] and knee arthroplasty[35] and as high as 80% in patients after liver and renal transplants.[11] Predisposing factors to long-term ICUAW include surgeries requiring long periods of postoperative bed rest or medical conditions that result in immobilization (*e.g.*, obesity, medical devices).[36] Other factors associated with persistent muscle weakness include older age, dementia, cancer diagnoses, malnutrition, social isolation, and preexisting functional immobility.[37]

Table 1 summarizes incidences reported in 10 studies, distinguishing between medical and surgical/trauma settings.[1,3,6,10,38–43] Most data derived from research in medical ICUs report an estimated ICUAW incidence of 25 to 31%. In the surgical ICU, 56 to 74% of patients acquire muscle weakness.[3,6] The higher incidence in the surgical ICU compared with the medical ICU is believed to be a consequence of pain, surgical muscle trauma, posttraumatic inflammation, and the lingering effects of anesthetics and NMBAs.[44]

Etiology and Mechanisms of Muscle Weakness Acquired in the Surgical Intensive Care Unit

ICUAW is typically a symmetric disease that can be induced by different mechanisms. The resulting weakness may be either transitory or long lasting (fig. 1). Critical illness polyneuropathy (CIP) is an acute axonal sensorimotor polyneuropathy[45] characterized by a reduction in the amplitudes of compound muscle action potentials and sensory nerve action potentials, with normal nerve conduction velocity.[8,46] Clinical signs, sensory signs in particular, are often unreliable in the acute stages of critical illness to clearly identify this condition. Therefore, electrophysiologic tests remain the definitive-standard tool for diagnosis of CIP.[47] CIP is most commonly associated with severe sepsis.[15] The incidence of CIP in patients with multiorgan failure is almost five times higher than in patients without multiorgan failure.[48]

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Table 1. Diagnostic Criteria and Incidence of ICU Muscle Weakness in Medical and Surgical ICUs

Authors	Type of Population	N	Setting	Main Outcome	Diagnosis of ICUAW	Reported Incidence of ICUAW
De Jonghe *et al.*[38]	Variable population	242	Not specified	To summarize the prospective clinical studies of neuromuscular abnormalities in ICU patients	MRC	36–70% in patients receiving steroids or NMBAs; 60% in patients with multiorgan failure
De Jonghe *et al.*[1]	All consecutive ICU patients without preexisting neuromuscular disease who underwent mechanical ventilation for ≥ 7 d were screened daily for awakening	95	Three medical and two surgical ICUs	Incidence and duration of ICUAP, risk factors for ICUAP, and comparative duration of mechanical ventilation between ICUAP and control patients	MRC < 48	25.3% (95% CI = 16.9–35.2%)
Ali *et al.*[10]	Adults requiring at least 5 d of mechanical ventilation without evidence of preexisting neuromuscular disease	136	Medical ICU	1. To test whether ICUAP is independently associated with increased mortality 2. To determine whether handgrip dynamometry is a concise measure of global strength and is independently associated with mortality	Average MRC < 4 in each muscle group (total MRC < 48) and handgrip dynamometry	25.7%
Schweickert *et al.*[39]	Sedated adults (≥ 18 yr of age) in the ICU who had been on mechanical ventilation for < 72 h, who were expected to continue for at least 24 h, and who met criteria for baseline functional independence	104	Medical ICU	1. Number of patients returning to independent functional status at hospital discharge 2. Duration of delirium and ventilator-free days during the first 28 d of hospital stay	MRC < 48 and handgrip dynamometry	31% at discharge in patients with early rehabilitation; 49% in control patients
Sharshar *et al.*[40]	Consecutive patients who were enrolled after > 7 d of mechanical ventilation.	115	Two medical, one surgical, and one medicosurgical ICUs	To assess whether the presence and severity of ICU-acquired paresis are associated with ICU and in-hospital mortality	MRC < 48	65% at day 1; 38.2% at day 7
Papazian *et al.*[41]	Patients presenting to 20 ICUs with an onset of severe ARDS within the previous 48 h	340	Not specified	90 d in-hospital mortality rate	MRC < 48	31.5–35.7% by ICU discharge
Routsi *et al.*[42]	Consecutive ICU patients with an APACHE II score ≥ 13	140	Medical/surgical ICU	To assess the efficacy of electrical muscle stimulation in preventing CIPNM in critically ill patients	MRC < 48	12.5% in patients with electrical muscle stimulation, 39.3% in patients without electrical muscle stimulation
Kasotakis *et al.*[6]	Patients admitted to the surgical ICU	113	Surgical ICU	To test whether the surgical ICU optimal mobility score predicts mortality and ICU and hospital length of stay	Grip strength	56%
Connolly *et al.*[3]	Patients aged 18 yr and older who had been invasively ventilated for ≥ 48 h	20	Medical/surgical ICU	To determine interobserver agreement and clinical predictive value of the MRC-SS test in critically ill patients	MRC < 48	73.9%
Hermans *et al.*[43]	Patients still in ICU on day 8 after admission	415	21.4% in medical ICU and 78.6% in surgical ICU	To determine acute outcomes, 1-yr mortality and costs of ICUAW among long-stay (≥ 8 d) ICU patients and to assess the impact of recovery of weakness at ICU discharge	MRC < 48	55%

A comparison of criteria and incidence of ICU muscle weakness in medical and surgical ICUs in the available literature. The incidence of muscle weakness is reported to be between 25 and 31% in medical ICUs. The incidence in surgical ICUs is reported to be between 56 and 74%, considerably higher than that of the medical ICUs. This higher incidence in the surgical ICU is believed to be a consequence of pain, surgical muscle trauma, posttraumatic inflammation, and the lingering effects of anesthetics and NMBAs.

APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CIPNM = critical illness polyneuropathy and myopathy; ICU = intensive care unit; ICUAP = ICU–acquired paresis; ICUAW = ICU–acquired weakness; MRC = Medical Research Council Scale for muscle strength; MRC-SS = MRC sum score; NMBA = neuromuscular-blocking agent.

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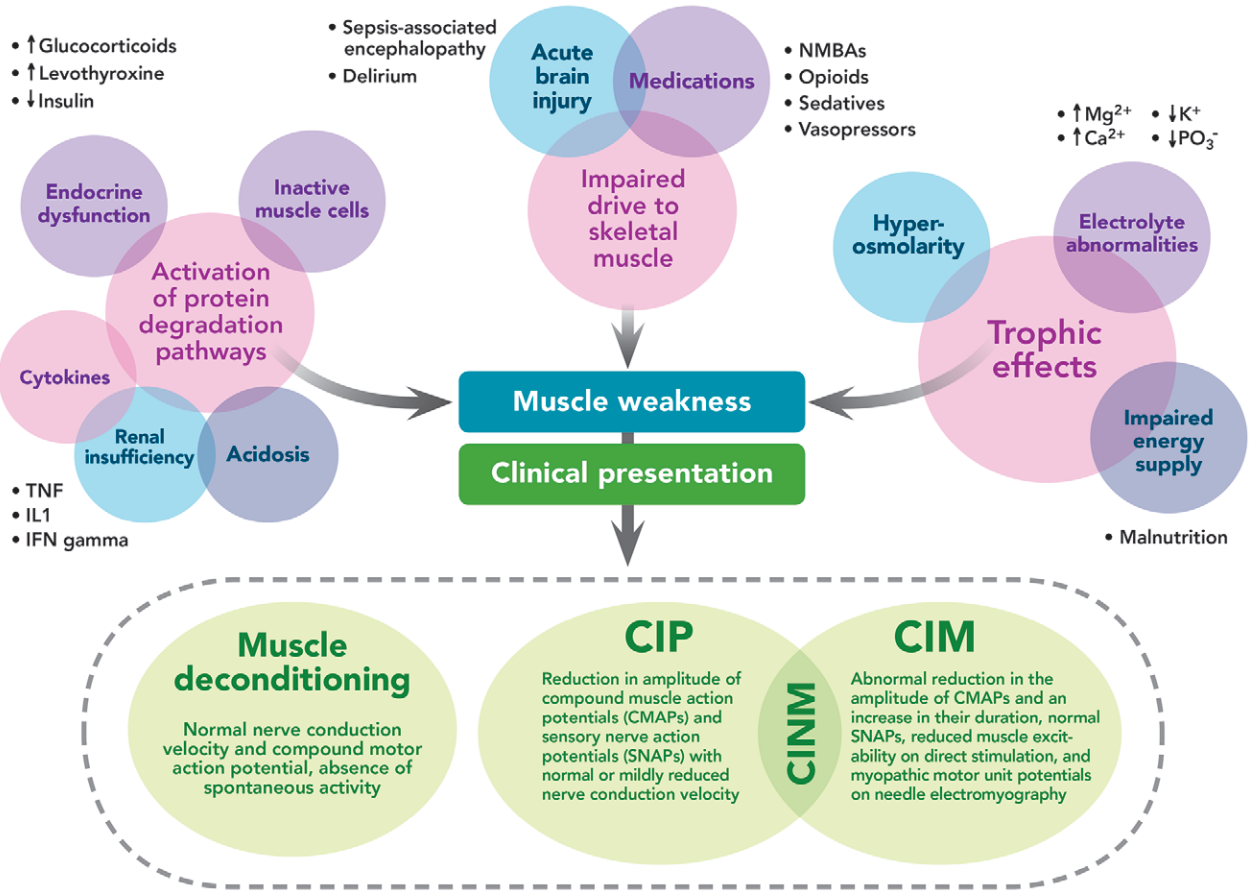

Fig. 1. Mechanisms of ICUAW can be subclassified into two main groups: ICUAW with electrophysiologic and histopathologic findings (CIP and CIM) and ICUAW with normal diagnostic studies. Muscle weakness in the ICU with normal electromyogram findings can be caused by many factors that produce a direct impairment of the muscle cell without necessarily affecting the neurogenic output. Activation of protein degradation with the ubiquitin–proteasome pathway, inflammatory mediators, and inactivity decrease muscle size and produce atrophy. Electrolyte and acid–base imbalances produce trophic effects and functional impairment of the muscle cell. Medications and delirium affect mental status and decrease cortical arousal promoting long periods of inactivity and muscle weakness. CIM = critical illness myopathy; CINM = critical illness neuromyopathy; CIP = critical illness polyneuropathy; CMAP = compound muscle action potential; ICU = intensive care unit; ICUAW = ICU–acquired weakness; IL = interleukin; IFN = interferon; NMBA = neuromuscular-blocking agent; TNF = tumor necrosis factor; SNAP = sensory nerve action potential.

Critical illness myopathy (CIM) is an acute primary myopathy not secondary to muscle denervation, with characteristic electrophysiologic and histologic features. Electrophysiologic studies typically report short duration, low-amplitude compound muscle action potentials with normal sensory nerve action potentials.[8,49] The definitive-standard test for CIM is muscle biopsy that further subclassifies this entity into cachectic myopathy, thick filament myopathy, and necrotizing myopathy.[8] The thick filament myopathy with loss of myosin filament can be a very early event occurring in the initial stage of critical illness.[50]

CIM is generalized and involves both limb and respiratory muscles, causing muscle weakness and paralysis, which are both clinically indistinguishable from that caused by CIP. Moreover, CIP and CIM can coexist,[51] a condition that has been called critical illness neuromyopathy (CINM).

Transitory Reductions in Muscle Strength

Transitory impairment of muscle strength occurs regularly in the perioperative period as a consequence of attempts of the anesthesiologist to improve surgical conditions. Anesthesia affects respiratory arousal through an impairment of diaphragmatic and upper airway muscle function along with an inability to protect the airway.[52,53] Respiratory arousal is defined as the arousal from sleep and other drug-induced or endogenous alterations of the mental status because of cumulative and progressive increases in stimuli related to breathing.[54] These stimuli are regulated by chemoreceptors that respond to changes in the partial pressures of oxygen and carbon dioxide,[55] sensors in the upper airway responsive to negative pressure generated by the respiratory pump,[56] and neural drive through cortical stimulation.[57] During the perioperative period, respiratory arousal is dampened by sedation, anesthesia, opioids, and endogenous impairment

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of consciousness. Consequently, the total level of stimulation to respiratory muscles decreases, and the upper airway is more vulnerable to collapse and respiratory failure.[54] Upper airway muscles are generally more affected by sleep, anesthetics, and sedatives than respiratory pump muscles.[54]

Neuromuscular-blocking Agents, Anesthetics, and Opioids

In the surgical ICU, NMBAs are given to patients with increased intracranial pressure[58] and are also used to reduce stress and strain on the lung in patients with severe acute respiratory distress syndrome (ARDS).[59] The use of NMBAs in the ICU is associated with higher rates of delirium (67 to 73%),[60] prolonged muscle weakness, and myopathy.[29,33] The lingering effects of NMBAs after surgery can also result in residual neuromuscular blockade, which delays recovery from both anesthesia and surgery.[29,30] Postoperative residual paralysis prolongs the impairment in function of respiratory and peripheral muscles[61] and transiently increases the incidence and severity of symptoms of muscle weakness[62] but does not increase the incidence of ICUAW as long as the NMBA is no longer given postoperatively in the ICU.

Continuous administration of NMBAs has similar effects on muscle physiology as denervation,[63,64] which increases the risk of muscle atrophy (fig. 1). Mechanical ventilation is nearly universally accompanied by the administration of large doses of anesthetics[65] that further increase the incidence of ICU-acquired delirium and weakness, especially in older surgical patients.[39,66] Furthermore, patients with sepsis are particularly vulnerable to the weakness inducing effects of NMBAs. Sepsis itself is an independent predictor of CINM.[67]

Prolonged use of aminosteroidal NMBAs can result in muscle weakness that lasts for up to 7 days after termination of administration.[68] Preclinical data also indicate that aminosteroidal NMBAs can worsen ventilator-induced diaphragmatic injury.[69] This may exacerbate weaning-related concerns in those with neurologic compromise.

Despite the negative outcomes associated with NMBA administration, it is important to consider that short-term infusion of NMBAs may facilitate protective mechanical ventilator treatment in patients with severe ARDS, without necessarily increasing the risk of ICUAW.[41] Thus, short-term use of NMBAs may be considered as a lung-protective adjuvant in early ARDS if sedatives and opioids do not allow control of the excessive respiratory drive.[67]

Procedural pain (*e.g.*, extubation, chest tube insertion or removal, wound drain removal, and arterial or central venous line insertion) is common in the SICU and requires further analgesic interventions.[35,70,71] Opioid analgesics are of particular importance to this discussion, because they are known to cause respiratory depression and can impair ventilation because of their effects on the respiratory muscles. Studies have shown that opioids increase pulmonary resistance *via* cholinergic effects on the smooth muscle,[72] reduce chest wall compliance, and reduce phrenic nerve and diaphragmatic muscle activity.[73–75] Together these effects reduce minute ventilation.[76] This is not to say that opioids should not be used. Although opioids contribute to the development of muscle weakness, conversely, optimal pain management can improve pulmonary function,[77] as severe postoperative pain results in shallow breathing, atelectasis, and delayed early mobilization of the patient.[78] Thus, the authors advocate judicious use of opioid titrated to effect and regular review of the necessity for continued prescription in the interest of improving patient outcomes in the SICU.

Other Mechanisms of Transient Muscle Weakness in the ICU

Figure 1 shows additional factors known to contribute to transitory muscle weakness, including inflammatory mediators,[79] delirium,[80] electrolytes disorders (hypermagnesemia, hypokalemia, hypercalcemia, hypophosphatemia), and endocrine dysfunction.[81–83] Hyperkalemia occurs frequently with rhabdomyolysis, propofol infusion syndrome, hyperthermic malignant syndromes, succinylcholine administration, and renal failure.[84,85] Other electrolyte disorders such as hypophosphatemia with hypomagnesemia are also common with refeeding syndrome in a previously malnourished patient.[86,87]

Endocrine abnormalities such as thyrotoxic periodic paralysis can cause paralysis associated with hypokalemia in absence of a deficit in total body potassium. The prevalence is low among Caucasians (0.1 to 0.2%), but 10 times greater in those of Asian origin.[81] It is sporadic in 95% of cases and mainly associated not only with autoimmune thyrotoxicosis (Graves disease) but also with thyroid stimulating hormone–secreting pituitary tumors, amiodarone-induced thyrotoxicosis, lymphocytic thyroiditis, *etc*.[81] In fact, any cause of thyrotoxicosis, including excessive thyroid hormone replacement therapy, can trigger paralysis in susceptible patients. Metabolic disorders such as acute intermittent porphyria can cause peripheral neuropathy, mostly motor in nature and resembling Guillain–Barré syndrome.[88] Acute intermittent porphyria presents with severe abdominal pain, nausea, vomiting, constipation, and symptoms of ileus mimicking a surgical emergency.[88] It can be triggered by exposure to porphyrinogenic drugs such as ketamine, thiopental, clonidine, propafenone, carbamazepine, phenytoin, clonazepam, ketorolac, quetiapine, fluconazole, clindamycin, and amiodarone.[88]

Clinically Significant Muscle Weakness Leading to Impaired Functional Independence

There is a grey zone between temporary and persistent muscle weakness: long-term exposure to evoked temporary muscle weakness in the ICU translates to clinically meaningful ICUAW.

Mechanical Unloading

In the surgical ICU, mechanical and/or pharmacologic unloading refers to the reduction in physical activity of

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the peripheral skeletal, postural, and respiratory muscles as a result of bed rest, joint immobilization, limb suspension, microgravity, and mechanical ventilation.[89] Mechanical unloading together with reduced neural activation result in the skeletal muscle wasting otherwise known as disuse.[89,90] The loss of muscle mass and fiber cross-sectional area is well documented in both rodent and human models of mechanical unloading.[90] The rate and extent of muscle loss seem to be dependent on both the muscle type and the degree of inactivity. In rodent models of hind limb immobilization, for example, muscle loss is generally greater in the extensor muscles of the ankle (soleus and gastrocnemius).[91,92] This pattern of muscle loss is also seen in humans with lower limb immobilization after ankle fracture.[93] Furthermore, in humans, there is a preferential loss of type I muscle fibers,[94,95] the muscle type most used in activities of daily living, a finding particularly relevant when considering functional independence outcomes after ICU stay. This pattern may be exacerbated among those with central neurologic injury.[96] A disruption to the equilibrium of protein synthesis and degradation underlies the pathophysiology of disuse atrophy resulting in a net loss of muscle protein.

Impairment of Protein Synthesis

Although there is evidence from human studies demonstrating that the basal rate of protein synthesis begins to decrease in the immediate period after disuse,[97,98] the cellular mechanisms responsible for this reduction in protein synthesis are poorly understood.[90] As such, several immobilization-associated pathways (glycogen synthase kinase-3β activity, the elongation factor 2 pathway, and ribosome biogenesis)[90,99] are currently being explored in the context of ICUAW with limited investigation.

It is important to stress that the overall contribution of decreased protein synthesis on muscle atrophy in mechanical unloading is minimal, and reduced protein synthesis alone is generally considered to be an inadequate explanation for the mechanism of atrophy. In an excellent review of this topic, Sandri[100] explains that the size of a postmitotic cell stems from a balance between protein synthesis and degradation and that a reduction in protein synthesis cannot be considered to be the sole mechanism behind muscle atrophy. Under conditions of protein synthesis inhibition, the total protein content of the cell is affected by protein half-life, which itself is dependent on basal protein degradation rates. Thus, in circumstances of reduced protein synthesis, which critically ill patients commonly experience,[101] muscle cell size ultimately depends on proteolysis more than it does under conditions of normal protein synthesis.[100] In early systemic inflammation, for example, the proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interferon-γ, and interleukin (IL)-1 increase ubiquitin gene transcripts and thus enhance skeletal muscle catabolism.[102]

Promotion of Proteolysis

Activation of several proteolytic mechanisms occurs with mechanical unloading and as a consequence of critical illness as described in figure 1. Taken together, these processes complementarily lead to the breakdown of muscle proteins that leads to significant muscle atrophy in as little as 2 to 5 days after unloading.[34,89,103]

The most prominent of these degenerative pathways is the ubiquitin–proteasome system (UPS).[89,90] The changes in muscle activity stimulate the UPS system to remove sarcomeric proteins. Muscle disuse increases the expression of key gene products that regulate this pathway. Muscle atrophy occurs as a result of increased conjugation of ubiquitin to muscle proteins, increased proteasomal adenosine triphosphate–dependent activity, increased proteolysis, and up-regulation of transcripts encoding key components of the UPS pathway (*e.g.*, ubiquitin, ubiquitin-ligases and proteasome subunits).[100,104] MAFbx/atrogin1 and MuRF1 are two E3 ligases that are of particular interest, because they are up-regulated in all conditions of muscle wasting, including disuse atrophy.[105] An increased expression of these gene products has been demonstrated in the diaphragms of mechanically ventilated rodents and humans[106–108] and in the limb muscles of humans after bed rest, lower limb suspension, or knee immobilization.[103,109–112] As expected, up-regulation of components of the ubiquitin pathway leads to increased conjugation between ubiquitin and muscle proteins in humans. This coupled with the finding that mechanical unloading increases the proteolytic activity of the 20S- and 26S-proteasome complexes results in an increased breakdown of ubiquitin-conjugated proteins.[106,108,110] Furthermore, muscle proteases are activated under disuse conditions. In 2008, Levine *et al.*[113] first discovered that caspase-3 mRNA expression is increased in human diaphragm muscles during mechanical ventilation, a finding that has since been corroborated in rodent diaphragm and limb muscles.[114,115] Mechanical unloading has also been shown to induce up-regulation of another protease, calpain, in the both diaphragm and limb muscles.[115–117]

Likewise, the autophagy–lysosomal system is emerging as an important pathway that is modulated by critical illness[118,119] and muscle disuse.[94,107,116] Autophagy is a constitutively active catabolic process in the skeletal muscle, which is up-regulated under conditions of fasting, oxidative stress, and denervation, leading to muscle protein degradation.[120,121] Studies have demonstrated that lysosomal degradation contributes to protein breakdown in denervated muscle,[122] and there is a significant up-regulation of lysosomal proteases, such as cathepsin L, under conditions of atrophy.[123] Myofiber atrophy resulting from *in vivo* overexpression of a constitutively active FoxO3 (a transcription factor that promotes cell death), for example, is dependent on autophagy, while siRNA knockdown of LC3 (a protein that is involved in autophagosome development) has been shown to partially prevent this FoxO3-mediated muscle

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atrophy.[118,124] Genetic models have also confirmed the role of autophagy in muscle atrophy.[118] Oxidative stress induced by a muscle-specific mutant superoxide dismutase protein ($SOD1^{G93A}$) has been shown to cause muscle loss as a result of autophagy, whereas attenuation of autophagy by knockdown of LC3 in $SOD1^{G93A}$ transgenic mice results in maintenance of muscle mass.

Although autophagy is a catabolic process involved in the breakdown of cells, recent studies suggest that it may be important in the maintenance of muscle mass in critically ill patients because autophagy also plays a crucial role in cellular homeostasis by ensuring the removal of damaged and dysfunctional intracellular proteins and organelles.[125] The essential role autophagy in muscle homeostasis is exemplified by the phenotypes of mice with muscle-specific inactivation of genes encoding autophagy-related proteins.[118] Ablation of Atg7, a crucial component in autophagosome formation, results in disorganized sarcomeres that lead to myofiber degeneration.[126] This manifests as muscle atrophy and weakness in Atg7-null mice. Moreover, fasting- and denervation-induced atrophy was exacerbated in Atg7-null mice.[127] This beneficial effect of autophagy has also been observed in humans. Autophagy is induced by both endurance and resistance exercise.[100,128,129] Autophagy also mediates the metabolic beneficial effects of exercise on glucose homeostasis.[100,130] This activation of autophagy during exercise is believed to be an adaptive response for the removal of proteins and organelles damaged by exercise or a mechanism to provide energy for sustained muscle contraction.[100] These favorable effects of autophagy have even been shown to benefit critically ill patients. In a large subanalysis of the EPaNIC trial, Hermans *et al.*[131] found that critically ill patients receiving early parenteral nutrition were more likely to develop muscle weakness within 9 days of randomization than those receiving late parenteral nutrition. In 58 patients with muscle weakness, a significant inverse association between autophagy and the development of ICUAW was identified.[131,132]

Sepsis

Muscle weakness may be clinically apparent on admission to the ICU, but because clinical assessments require patient arousal and collaboration, the diagnosis is often delayed in patients with sepsis[133] as the appropriate initial management of sepsis is rightly prioritized.[134] Patients with sepsis experience skeletal and respiratory muscle wasting and weakness more frequently than patients without sepsis.[44,79,135–137] This weakness results from the effects of inflammatory markers; immobilization; impaired oxygen delivery; and effects of sedation, opioids, and neuromuscular blockade. Furthermore, septic encephalopathy often renders patients immobile, thus compounding the risk of developing ICUAW.[135]

Proinflammatory cytokines have both direct and indirect effects on signaling pathways that regulate muscle mass.[138,139] TNF-α, interferon-γ, and IL-1 increase ubiquitin gene transcripts and thus enhance the skeletal muscle catabolism.[102] IL-6 has drawn particular interest because of its pleiotropic effects[140] and as such has been dubbed the "double-edged sword" in relation to acquired muscle weakness. On one hand, IL-6 is a proinflammatory cytokine, traditionally associated with control and coordination of immune responses.[141] In IL-6 deficient mice, for example, the inflammatory acute phase response after infection is severely blunted.[142] Animal models of inflammation and tumor-induced cachexia provided early experimental evidence of the negative effects of IL-6. Inhibition of the increased IL-6 levels that exist in these models was shown to have a protective effect on weight loss and muscle wasting.[143,144] High doses of IL-6 or prolonged exposure have been shown to increase muscle catabolism.[145] Moreover, transgenic mice overexpressing human IL-6 show severe muscle atrophy by the age of 10 weeks, along with an increased activation of myofiber lysosomal enzymes and proteasomal subunit expression, suggesting that these mice have increased basal rates of protein degradation.[146] Inhibition of IL-6 by neutralizing antibodies in these transgenic mice resulted in a complete reversal of the muscular atrophy.[147] However, other studies have found no association between IL-6 levels and muscle atrophy,[148,149] suggesting that it is the combination of IL-6 with other endogenous mediators, such as TNF-α and IL-1,that produces this catabolic response in the muscles under conditions of sepsis.[102]

Interestingly, in contrast to the findings mentioned in Sepsis (paragraph 2), recent studies have identified IL-6 as a myokine that promotes muscle growth and regeneration.[140,150] The discovery of IL-6 as a myokine was an incidental finding after the observation that it increased exponentially and proportionally in response to exercise and the amount of muscle mass engaged in exercise.[140,151] IL-6 produced after an acute stimulus—without previous increase in TNF-α[152]—has a positive impact on the proliferative capacity of muscle progenitor cells.[140] It promotes muscle hypertrophy by activating satellite cells and by stimulating myoblast differentiation and fusion.[153] Confirming that IL-6 plays a role in muscle hypertrophy, IL-6 knockout mice have been shown to have an impaired hypertrophic response to muscle overloading.[150] This hypertrophic effect of IL-6 in response to overloading has also been confirmed in human muscle and electrically stimulated human myocytes.[151,154] Therefore, transient production of IL-6 after mechanical loading in critically ill patients may actually facilitate muscle regeneration and hypertrophy in contrast to the catabolic effects of sustained IL-6 production seen in sepsis.[140]

Mechanical Ventilation

Prolonged mechanical ventilation can lead to barotrauma, volutrauma, and atelectrauma, as well as ventilator-induced diaphragmatic injury.[155] Diaphragmatic atrophy that can be apparent in as little as 48 h, as the work of breathing is assumed by a ventilator,[34] and the magnitude of ventilator-induced

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diaphragmatic injury is associated with the level of support provided by the ventilator: preclinical data show that volume control compared with pressure support ventilation leads to more severe diaphragmatic weakness. On the biochemical level, unloading of the respiratory muscles by mechanical ventilation promotes crosstalk and up-regulation of the calpain, caspase-3, and UPSs that contribute to proteolysis that results in weakness and atrophy.[89,90,156,157]

Nutrition

Critically ill patients commonly have a poor nutritional status that predicts adverse outcome. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery.[5,158] Poor nutritional status has long been associated with greater morbidity and mortality, particularly in the surgical population.[159] Malnutrition is associated with impaired immune function, reduced ventilatory drive, weakened respiratory muscles, and prolonged ventilator dependence.[160] Critical illness induces a catabolic state in which an imbalance between protein synthesis and degradation leads to cellular death and muscle atrophy, otherwise known as sarcopenia, which in turn is associated with poor nutritional status.[5,137] The consequences of poor nutritional status in ICU patients are more severe compared with the catabolic state induced by fasting in healthy persons because this calorific debt is often superimposed on inflammatory and endocrine responses as well as immobilization.[161]

Although adequate nutrition in critically ill patients is important in the long term to negate the deleterious effects of a severe calorific debt, multiple studies have demonstrated that outcomes are also influenced by the mode of feeding and timing of feed initiation. Some studies indicate that early parenteral feeding may in fact promote greater levels of muscle wasting possibly because of inhibition of autophagy.[101,131,162] In a subanalysis of the EPaNIC trial, for example, the authors found a greater expression of markers of autophagy in the late parenteral nutrition group.[131] This suggests that the caloric restriction induced by late parenteral nutrition optimizes autophagic recycling of proteins with removal of toxic proteins and damaged cell organelles that may improve cell functioning.[132,163] Mitophagy induced by late parenteral nutrition may thus optimize cellular conditions in the muscle cells for effective muscle contraction and strength generation, possibly explaining the increased strength seen in the late parenteral nutrition group.[132] It is important to note that the EPaNIC study studied mostly cardiac surgery patients, of whom 50% stayed in the ICU for less than 3 days. In more severely ill patients, optimized energy supplementation with parenteral nutrition can reduce nosocomial infections, antibiotic usage, and time on mechanical ventilation.[164]

Steroids

Approximately 31% of ICU patients exposed to steroids develop ICUAW.[165] The association between steroid therapy and long-term functional impairment seems to be dose-dependent.[12] Large multicenter studies have identified both corticosteroid administration[1] and mean daily corticosteroid dose as strong predictors of ICUAW.[166] In a randomized controlled trial (RCT) of 180 patients with persistent ARDS, methylprednisolone treatment was found to improve cardiopulmonary parameters but also resulted in a higher rate of neuromuscular weakness.[167]

There is conflicting evidence regarding whether short-term use of steroids increases the risk of ICUAW in critically ill patients. Some data suggest that even a short-term steroid treatment in the ICU can lead to functional impairment.[166] Stipulated mechanisms include impairment of the muscle membrane causing lack of excitability and promotion of muscle catabolism resulting in an imbalance between protein synthesis and loss.[168–170]

There are equivocal data on the effects of steroids in septic shock on mortality. Although low-dose steroids do not affect mortality,[171,172] there is some evidence suggesting that disease entity–based subgroups of patients with septic shock may benefit from corticosteroids.[171] A recent retrospective cohort study demonstrated that a short course of methylprednisolone decreased treatment failure (defined as development of shock, need for mechanical ventilation, and death within 120 days) in patients with severe pneumonia.[171]

Corticosteroid treatment in critically ill patients should therefore be tailored to the presentation and disease severity. Short-term administration in the most critically ill patients may improve outcomes in certain critically ill populations; however, long-term administration can increase the risk of ICUAW.

Other Mechanisms Implicated in the Development of Muscle Weakness

Central Melanocortin System. The central melanocortin system plays a significant role in the pathogenesis of cachexia.[173] Stimulation of the melanocortin-4 receptor, which is expressed mainly in the brain, results in anorexia, weight loss, and an increased metabolic rate,[173] opening this pathway as a potential target in the prevention and treatment of muscle weakness.

Myostatin. Myostatin, a member of the transforming growth factor-β family, is known to inhibit muscle cell growth and differentiation as well as decrease protein synthesis.[174] These effects make myostatin an important target in the treatment and prevention of sarcopenia. Furthermore, *myostatin* gene mutations have been associated with increased muscle mass in humans.[175]

Vitamin D. The prevalence of low vitamin D levels is high among ICU patients.[176] A growing body of evidence suggests that low 25-hydroxy vitamin D levels are associated with a host of negative outcomes in critically ill patients, including increased rates of infection and longer duration of hospital stay and mortality.[177] Of particular relevance to our discussion, low vitamin D levels are associated with sarcopenia. In

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fact, a recent surgical ICU study found that vitamin D levels are inversely associated with the duration of mechanical ventilation, which in itself is a marker of muscle weakness.[176]

Renin–Angiotensin System. The renin–angiotensin system (RAS) has extracardiac effects, some of which impact skeletal muscle. Angiotensin-converting enzyme (ACE) inhibitors are believed to have a beneficial effect on the skeletal muscle by limiting the effects of angiotensin II on the inflammatory response and the growth hormone/insulin-like growth factor (IGF)-1 axis.[173]

Critically ill patients are often hypotensive, which activates RAS. The activation of the RAS results in an increase in proinflammatory cytokines,[178] which in turn results in muscle protein degradation.[179] In humans, angiotensin II is known to induce IL-6[180] and matrix metalloproteinase secretion.[181] ACE inhibitors reverse these effects *in vitro* and *in vivo*.[173]

The RAS also has effects on the growth hormone/IGF-1 axis. IGF-1 is an anabolic hormone that increases protein synthesis in existing muscle fibers while also stimulating myogenesis.[173,182,183] Angiotensin II has been shown to be decrease IGF-1 levels, which leads to skeletal muscle wasting and reduced lean muscle mass.[183]

Functional Capacity and Outcomes. The frail phenotype is characterized by changes in mobility, muscle mass, nutritional status, strength, and endurance.[184] Frail patients may have a lower functional capacity and decreased ability to mobilize at baseline. Thus, they are vulnerable against severe physiologic stressors, predisposing them to functional dependence at discharge and death.

Sarcopenia is a key element of frailty, which translates to higher healthcare utilization and mortality. Sarcopenia in critically ill trauma patients as assessed by computed tomography (CT) is associated with mortality, ICU utilization, and loss of functional independence.[185] In a recent observational study, Puthucheary and Hart[185] found that muscle mass as assessed by abdominal CT scan was a significant predictor of outcome and discharge location after ICU admission. Further studies exploring this association are needed to identify whether the measurement of muscle mass on admission to the ICU can lead to better patient management as well as a more efficient allocation of healthcare resources. Thus, taking steps to identify and prevent ICUAW can improve functional outcomes on discharge, thus reducing the risk of subsequent readmission and improving outcomes during subsequent readmissions should they occur.

Future studies will demonstrate whether patients with and without impaired functional capacity at admission need to be treated differently to avoid acute care readmissions[18,20] and loss of functional independence after discharge.

Clinical Diagnosis of Muscle Weakness in the Surgical ICU

Figure 2 provides decision support for the differential diagnosis of ICUAW. The first step is a clinical examination at the bedside.[22] First, the patient's ability to cooperate with examination should be assessed, because the most valuable test to assess muscle strength depend on the patient's level of arousal and attention (fig. 3).[186]

In patients who cannot participate in volitional tests, drug effects (NMBAs, sedatives, opioids, and neuroleptics) and delirium need to be considered as possible mechanisms of muscle weakness. The Richmond agitation-sedation score, Glasgow coma score, and Confusion Assessment Method–ICU are useful tools to screen for cognitive impairments. A train-of-four ratio of more than or equal to 0.9 excludes a clinically significant impairment of neuromuscular transmission.[30,187]

In patients able to reliably participate in the process of manual muscle testing, a total Medical Research Council Scale for muscle strength (MRC) score of less than or equal to 48 suggests ICUAW.[3] Manual muscle testing—a subjective examination—has proven reliable in critically ill patients provided that strict guidelines on adequacy and standardized test procedures and positions are followed.[188] In contrast, grip strength testing is inferior to manual muscle testing in predicting morbidity and increased healthcare utilization related to ICUAW. Global muscle strength but not grip strength predicts mortality and length of stay in a general population in a surgical ICU.[189] As such, many experts perform manual muscle testing to identify patients with ICUAW in their clinical practices.[190]

An MRC score of less than 48 suggests the presence of ICUAW. Patients with altered mental status or with the evidence of ICUAW should undergo further workup to identify and correct the underlying disorder that may include the etiologies mentioned in figure 1. If the attempts to correct such disorders fail initially, imaging studies such as CT scan should be considered, especially in cases where focal neurologic symptoms are present or in persistent sepsis-associated encephalopathy.

The last resource that could be considered in cases of persistent muscle weakness is electrophysiologic testing (EPS; compound action potentials, nerve conduction velocity, electromyogram). EPS alone can specify the mechanism of ICUAW better than clinical examinations, but muscle biopsies may ultimately be required to specify the nosology of an underlying myopathy.

EPS and histopathology reports have shown that up to 100% of ICU patients exhibit the signs of CIP or CIM.[27,38,40,51,131,191–195] A systematic review reported CINM in 46% of patients; of these, CIP was present in 20% and CIM in 13%, whereas underlying pathology was unknown in 77.6%.[194] Our group found that in the SICU, CIP, CIM, and CINM were the cause of muscle weakness in only 38% of patients with sepsis.[133]

Electrophysiologic testing is limited by its predictive value for long-term outcomes.[196] The examination requires expert examiners, is time consuming, and can cause considerable discomfort to the awake patient.[190,196] However, the peroneal nerve test can be easily implemented in the ICU, and the results can almost be used interchangeably compared with complete electromyographic investigation for making diagnosis CIP/CIM.[48,197] Some data suggest that

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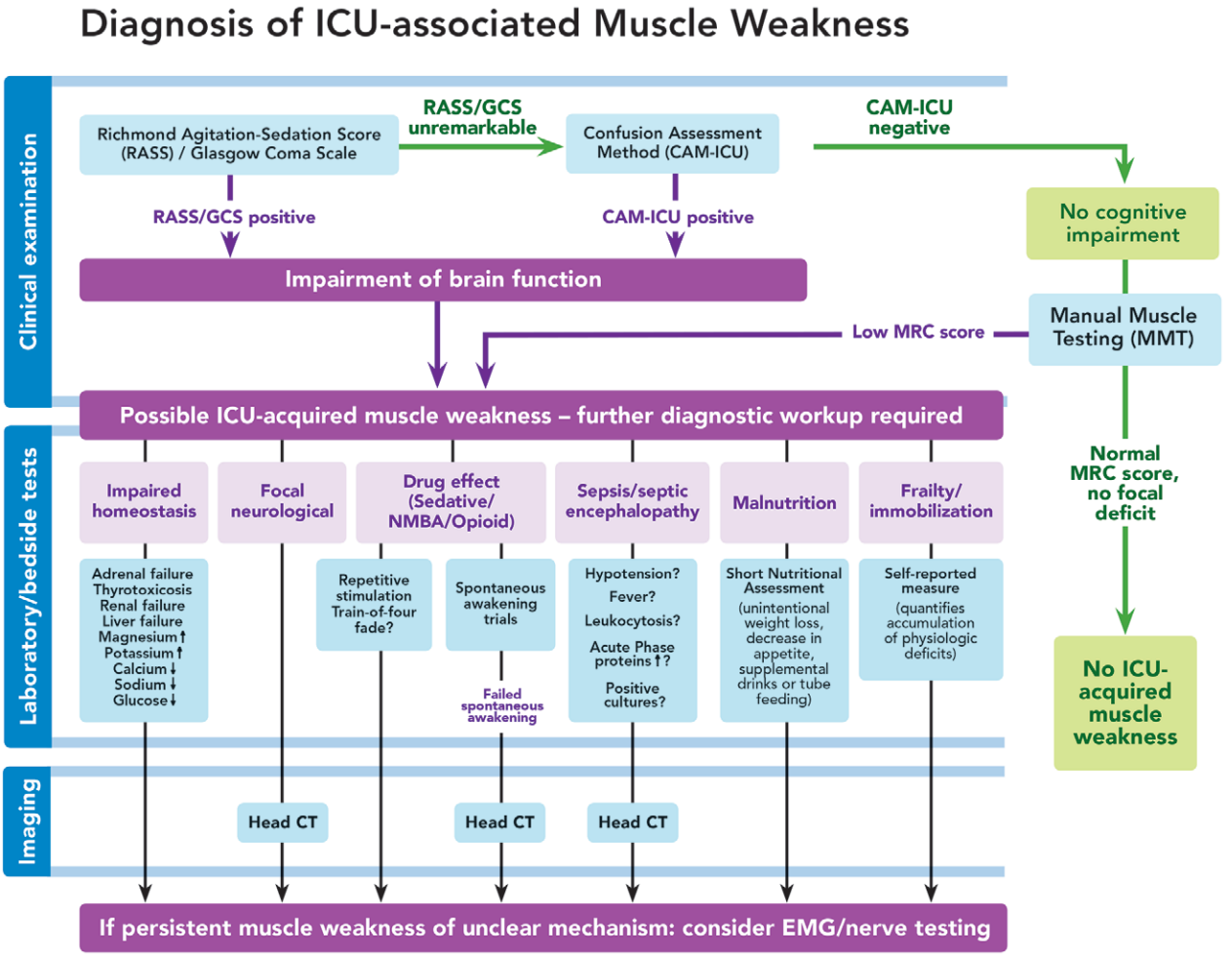

Fig. 2. Diagnosis of ICU-acquired muscles weakness. On daily clinical examination in the ICU, cognitive function needs to be assessed. Glasgow coma scale (GCS) should be assessed on admission of trauma patients; sedation and agitation level should be evaluated, and delirium screening should be conducted. In patients able to follow commands, manual muscle testing should be conducted, and a normal score (of ≥ 48 using the medical research council scale, 0 to 5, six muscle groups, bilateral testing) and absence of a focal motor deficit confirm the absence of ICU-acquired muscle weakness. Impaired mental status or a low MRC score dictate additional diagnostic workup for ICU-acquired muscle weakness that includes blood tests, point-of-care testing (train-of-four ratio), as well as a spontaneous awakening trial. Persistent neurologic deficit triggers advances imaging of the brain, and electrophysiologic testing (EMG, measurement of nerve conduction velocity) may be considered in patients with persistent, severe muscle weakness of unclear mechanism. CAM = Confusion Assessment Method; CT= computed tomography; EMG = electromyogram; ICU = intensive care unit; MRC = Medical Research Council scale; NMBA = neuromuscular-blocking agent.

identification of the underlying pathophysiology of persistent ICUAW is important, because CIP is a marker of persistent disability and delayed recovery, whereas CIM may lead to a better prognosis and a faster recovery than CIP.[198,199] A recent study has even suggested that early electrophysiologic testing in critical illness can predict long-term functional outcomes[198]; however, further research is required to ascertain whether this is feasible and worthwhile.

Prevention of ICU-acquired Muscle Weakness in SICU

Persistent muscle weakness can be prevented by using the multimodal approach illustrated in figure 4. The authors believe that to prevent an impairment of functional independence from ICUAW, muscle function should be evaluated and measured regularly as a part of the daily patient assessment. Recently, we proposed some strategies to prevent the development of acquired muscle weakness.[44] Table 2 breaks down these individual strategies and provides a summary of the strongest evidence and recommendations for each one.

Treat Sepsis as Early and Aggressively as Possible

The Surviving Sepsis campaign[233] popularized the concept of early goal-directed therapy in sepsis, including the early use of antibiotics and fluid resuscitation to maintain an adequate central venous pressure, mean arterial pressure, urine output,

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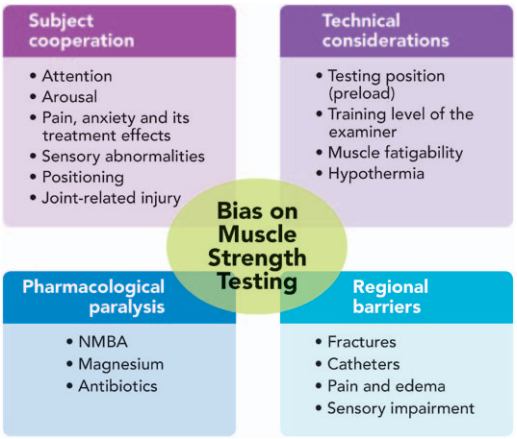

Fig. 3. Bias to clinical assessment of muscle strength. Clinical assessment of muscle strength is a volition-dependent examination, which requires adequate training of the examiner and consideration of perioperative barriers such as drug effects, pain, and medical devices. (Modified from the study by Waak *et al.*[186] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.) NMBA = neuromuscular-blocking agent.

and mixed venous saturation. Studies demonstrated that this approach reduced mortality, days of mechanical ventilation, and ICU[233] and hospital stay.[201,203] Although the recent Protocolized Care for Early Septic Shock (ProCESS)[134] and the Australasian Resuscitation in Sepsis Evaluation (ARISE)[204] have called into question the evidence for early goal-directed therapy in the management of sepsis, it is clear that early identification and appropriate treatment with antibiotics are the most important elements in the treatment of patients with sepsis.[234] Early treatment of sepsis may reduce the incidence of muscle weakness by preventing the development of inflammatory-mediated direct and indirect muscle damage and prompting an earlier return to physical activity and ambulation.[134,204] Furthermore, lung-protective ventilation with relatively low tidal volumes should be considered in patients with sepsis to reduce organ dysfunction and diminish the inflammatory response associated with atelectasis and ARDS.[200,202]

Optimize the Muscular Load

Mobilizing patients postoperatively is an important part of the recovery process. Point prevalence studies suggest that as few as 24% of mechanically ventilated patients and only 8% of patients with an endotracheal tube in the ICU are mobilized out of bed as a part of routine care.[235] Outcome studies in the medical ICU indicate that goal-directed early mobilization may lead to shorter duration of delirium, less mechanical ventilation time, fewer days in the ICU, reduced hospital length of stay, and better functional independence at hospital discharge.[9,44,205] Physical therapy with ergometry during ICU stay, for example, has been shown to improve functional outcomes as assessed by the 6-min walking distance and the isometric force of the lower limbs muscles[206] at

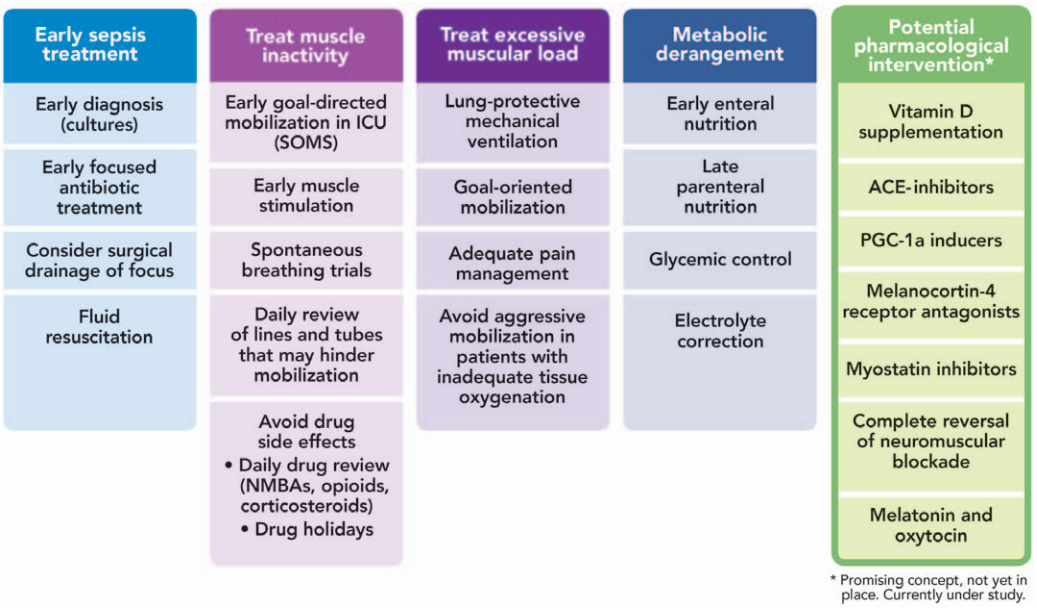

Fig. 4. Prevention of ICU-acquired muscle weakness. Early and aggressive sepsis treatment requires adequate diagnostic procedures to identify its mechanism, as well as early treatment with antibiotics, fluid resuscitation, and in the surgical ICU often a surgical intervention to drain the focus. It is imperative to optimize the drive to the skeletal muscles; both inactivity and excessive drive to the skeletal muscles can lead to muscle weakness by atrophy and injury. Metabolic derangement needs to be prevented to provide an optimal homeostasis for the muscle to recovery during the highest acuity levels of critical illness. Future studies will address the effectiveness of pharmacologic pathways to prevent ICU-acquired muscle weakness.[186] ACE = angiotensin-converting enzyme; ICU = intensive care unit; NMBA = neuromuscular-blocking agent; PGC = PPAR Gamma Coactivator; SOMS = surgical optimal mobilization score.

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Table 2. Recommendations for Prevention of ICU-acquired Muscle Weakness

	Study Design/ Sample Size	Setting	Intervention	Muscle Weakness	ICU LOS	Hospital LOS	Mechanical Ventilation (Duration or Weaning)	Mortality	Level*	Grade†
Aggressive treatment of sepsis										
Ranieri *et al.*[200]	RCT/44 patients (37 completed)	Medical and surgical ICU	Protective (low tidal) mechanical ventilation *vs.* conventional	N/R	N/R	N/R	↓ (8 d less)‡	↓ (38 *vs.* 58%)	B	IIA
Rivers *et al.*[201]	RCT/263 patients	Mostly medical patients, but also surgical	6 h of early goal-directed therapy *vs.* standard therapy	N/R	N/R	No difference	No difference	↓ (30.5 *vs.* 46.5%)‡	B	
Eisner *et al.*[202]	RCT/902 patients	Medical and surgical patients	Protective (low tidal) mechanical ventilation *vs.* Conventional	N/R	N/R	N/R	Proportion of patients achieving unassisted breathing by day 28 (62 *vs.* 52%)‡	↓ (31 *vs.* 40%)‡	B	
Trzeciak *et al.*[203]	Historical control trial/38 patients	Medical patients sent to ICU directly from ER	Early goal-directed therapy *vs.* standard therapy	N/R	↓ (1.8 *vs.* 4.2 d)	↓ (9 *vs.* 13 d)	N/R	↓ (18.2 *vs.* 43.8%)	B	
Yealy *et al.*[134]	RCT/1341 patients	Mostly medical patients	Protocol-based early goal-directed therapy *vs.* protocol-based standard therapy *vs.* usual care	N/R	No difference	No difference	No difference	No difference	B	
ARISE Investigators; ANZICS Clinical Trials Group[204]	RCT/1600 patients	Medical patients sent to ICU directly from ER	Early goal-directed therapy *vs.* usual care	N/R	No difference	No difference	No difference	No difference	B	
Optimize the muscular load: early (< 48 h) mobilization										
Kangas *et al.*[205]	RCT/50 patients	Surgical patients	Early movement of the ankle in a brace *vs.* Achilles tendon immobilization in tension using a below-knee cast with the ankle in a neutral position for 6 wk	Excellent to good isokinetic calf scores in the early movement group (56 *vs.* 29%)	N/R	N/R	N/R	N/R	B	IIA
Schweickert *et al.*[39]	Prospective RCT/104	Medical ICU	Progressive physical and occupational therapy *vs.* standard physical therapy	↓ (35 *vs.* 49%)	↓ (5.9 *vs.* 7.9 days)	No difference	↓ (3.4 *vs.* 6.1 days)‡	↓ (18 *vs.* 25 %)	B	
Burtin *et al.*[206]	Prospective RCT/90	Medical and surgical ICU	Standard PT mobilization plus cycling exercise	Improved quadriceps force at hospital discharge‡	No difference	↓ (36 *vs.* 40 d)	No difference	↓ (8 *vs.* 10%)	B	
Routsi *et al.*[42]	RCT/140 patients	Medical and surgical ICU	Electrical muscle stimulation to prevent CIPNM	MRC score improved (58 *vs.* 52)‡	↓ (14 *vs.* 22 d)	N/R	↓ (1 *vs.* 3 d)‡	No difference	B	
Keep the respiratory muscles moving										
Spontaneous breaths during mechanical ventilation										
Rathgeber *et al.*.[207]	Prospective controlled trial/596 patients	Surgical ICU	Biphasic positive airway pressure ventilation *vs.* synchronized intermittent mandatory ventilation *vs.* assist/controlled mandatory ventilation	N/R	N/R	N/R	↓ (10.1 *vs.*14.7 *vs.* 13.2 h)‡	N/R	B	IIA

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Table 2. (*Continued*)

	Study Design/ Sample Size	Setting	Intervention	Muscle Weakness	ICU LOS	Hospital LOS	Mechanical Ventilation (Duration or Weaning)	Mortality	Level*	Grade†
Putensen *et al.*[208]	RCT/30 patients	Trauma ICU	Airway pressure release ventilation with spontaneous breathing *vs.* pressure support controlled ventilation	N/R	↓ (23 *vs.* 30 d)‡	N/R	↓ (15 *vs.* 21 d)‡	No difference	B	
Protective mechanical ventilation										
Amato *et al.*[209]	RCT/53 patients	Medical and surgical ICU	Protective (low tidal) mechanical ventilation *vs.* conventional	N/R	N/R	N/R	Early weaning (66 *vs.* 29%)‡	↓ (38 *vs.* 71 %)‡	B	I
ARDS Network[210]	RCT/861 patients	Medical and surgical ICU	Protective (low tidal) mechanical ventilation *vs.* conventional	N/R	N/R	N/R	↓ (2 d less)‡	↓ (31 *vs.* 39.8%)‡	B	
Maxwell *et al.*[211]	RCT/63 patients	Surgical or trauma ICU	Low tidal volume ventilation *vs.* APRV	N/R	↓ (14.18 *vs.* 16.47 d)	N/R	↓ (8 *vs.* 10.49 d)	No difference	B	
Holiday periods										
Kress *et al.*[212]	RCT/128 patients	Medical ICU	Daily interruption *vs.* standard interruption of sedative drug infusion	N/R	↓ (3.5 d less)‡	↓ (13.3 *vs.* 16.9 d)	↓ (4.9 *vs.* 7.3 d)‡	↓ (36 *vs.* 46.7%)	B	I
Girard *et al.*[66]	RCT/336 patients	Medical ICU	Daily spontaneous awakening trial followed by a spontaneous breathing trial *vs.* sedation per usual care plus a daily spontaneous breathing trial	N/R	↓ (9.1 *vs.* 12.9 d)‡	↓ (14.9 *vs.* 19.2 d)‡	Ventilator-free days within 28-d study period): ↑ (14.7 *vs.* 11.6 d; mean increase 3.1 d)‡	↓ (44 *vs.* 58%)‡	B	
Robinson *et al.*[213]	RCT/143 patients	Surgical ICU	Daily interruption *vs.* standard interruption	N/R	↓ (4.1 *vs.* 5.9 d)	↓ (12 *vs.* 18 d)‡	↓ (1.2 *vs.* 3.2 d)‡	↓ (14.7 *vs.* 17.6%)	B	
Papazian *et al.*[41]	RCT/340 patients	Medical and surgical ICU	Short period of cisatracurium besylate *vs.* placebo	No difference	N/R	Days outside the ICU:↑ (47.7 *vs.* 33.5 d)‡	Ventilator free days (at 90 d): ↑ (10.6 *vs.* 8.5 d)‡	At 90 d: ↓ (30.8 *vs.* 44.6%)‡	B	
Mehta *et al.*[214]	RCT/430 patients	Medical and surgical ICU	Protocolized sedation plus daily sedation interruption *vs.* protocolized sedation	N/R	No difference	No difference	In surgical and trauma patients: ↓ (6 *vs.* 13 d)‡	N/R	B	
Optimal nutrition										
Enteral nutrition										
Singh *et al.*[215]	RCT/43 patients	Surgical ICU	Feeding jejunostomy from 12 h postoperatively *vs.* control	N/R	N/R	No difference	N/R	No difference	B	IIB
Marik and Zaloga[216]	Systematic review/15 RCT	Surgical or trauma ICU	Early *vs.* delayed enteral nutrition	N/R	N/R	↓ (2.2 d less; in trauma/ head injury/ burn patients 4.04 d less)‡	N/R	↓ (8 *vs.* 11.5%)	B	
Minard *et al.*[217]	RCT/30 patients	Trauma ICU	Early *vs.* delayed enteral feedings	N/R	No difference	No difference	No difference	↓ (8 *vs.* 27%)‡	B	

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Table 2. (*Continued*)

	Study Design/ Sample Size	Setting	Intervention	Muscle Weakness	ICU LOS	Hospital LOS	Mechanical Ventilation (Duration or Weaning)	Mortality	Level*	Grade†
Lewis *et al.*[218]	Systematic review and metanalysis/ 837 patients	Surgical patients	Enteral feeding started within 24 h after surgery *vs.* nil by mouth management in elective gastrointestinal surgery	N/R	N/R	↓ (10.4 *vs.* 12.9 d)‡	N/R	↓ (7 *vs.* 13%)	A	
Braunschweig *et al.*[219]	Metanalysis/ 27 studies; 1,828 patients	Medical and surgical patients	Parenteral nutrition *vs.* tube feeding *vs.* standard care	N/R	N/R	N/R	N/R	↑ In standard of care	A	
Heyland *et al.*[220]	Systematic review/8 RCT	Medical and surgical ICU	Early *vs.* delayed enteral nutrition or intravenous fluids	N/R	No difference	No difference	N/R	↓ (6.3 *vs.* 14.6%)	B	
Dvorak *et al.*[221]	RCT/23 patients (17 patients included in analysis)	Trauma ICU	Early *vs.* late enteral feeding	N/R	N/R	↑ (53 *vs.* 37.9 d)	↑ (763 *vs.* 502 h)	N/R	B	
Peck *et al.*[222]	RCT/95 patients eligible (data analyzed from 27 patients)	Trauma (burn) ICU	Early *vs.* late enteral feeding on postburn metabolism	N/R	↑ (40 *vs.* 37 d)	No difference	↑ (32 *vs.* 23 d)	↓ (28 *vs.* 38%)	B	
Artinian *et al.*[223]	Retrospective cohort/4049 patients	Medical ICU	Early *vs.* delayed enteral nutrition	N/R	↑ (10.9 *vs.* 10.2 d)‡	N/R	No difference	↓ (28.7 *vs.* 33.5%)‡	C	
Harvey *et al.*[224]	RCT/2400 patients	Medical and surgical ICU	Parenteral *vs.* enteral nutrition	N/R	No difference	No difference	No difference	↓ (33.1 *vs.* 34.2%)	B	
Parenteral nutrition										
Casaer *et al.*[162]	RCT/4640 patients	ICU	Late *vs.* early parenteral nutrition	N/R	↓ (3 *vs.* 4 d)‡	↓ (14 *vs.* 16 d)‡	Requiring > 2 d of mechanical ventilation: ↓ (36.3 *vs.* 40.2%)‡	No difference	B	IIB
Hermans *et al.*[131]	RCT/600 patients	Mostly surgical but also medical ICU	Late *vs.* early parenteral nutrition	↓ (34 *vs.* 43 %)‡	↓ (11 *vs.* 13 d)‡	↓ (27 *vs.* 32 d)	↓ (6 *vs.* 7 d)	↑ (11 *vs.* 9%)	B	
Heidegger *et al.*[164]	RCT/305 patients	Surgical and medical ICU	Supplemental parenteral nutrition with enteral nutrition *vs.* enteral nutrition alone from day 4 to 8 in the ICU	N/R	No difference	No difference	No difference	↓ (13 *vs.* 18%)	B	
Doig *et al.*[225]	RCT/1,372 patients	Surgical and medical ICU	Early parenteral nutrition within 24 h after ICU admission *vs.* standard therapy	N/R	↓ (8.6 *vs.* 9.3 d)	No difference	↓(7.26 *vs.* 7.73 d per 10 patient × ICU days)‡	↓ (21.5 *vs.* 22.8%)	B	
Tight glycemic control										
van den Berghe *et al.*[193]	RCT/1548 patients (preplanned subanalysis of patients still in ICU on day 7: 405 patients)	Surgical ICU	Intensive insulin therapy *vs.* conventional management	↓ (25 *vs.* 49%)‡	↓ (14 *vs.* 15 d)‡	N/R	↓ (11 *vs.* 13 d)‡	↓ (12 *vs.* 21%)‡	B	III

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Table 2. (*Continued*)

	Study Design/ Sample Size	Setting	Intervention	Muscle Weakness	ICU LOS	Hospital LOS	Mechanical Ventilation (Duration or Weaning)	Mortality	Level*	Grade†
Brunkhorst *et al.*[226]	RCT/537	Medical and surgical ICU	Intensive insulin therapy *vs.* conventional management	N/R	↑ (16 *vs.* 14 d)	N/R	No difference	↑ (39.7 *vs.* 35.4%)	B	
Wiener *et al.*[227]	Meta-analysis/ 34 trials; 29 RCTs contributed data	Medical and surgical ICU	Intensive insulin therapy *vs.* conventional management	N/R	N/R	N/R	N/R	↓ (21.6 *vs.* 23.3%)	A	
Griesdale *et al.*[228]	Meta-analysis/26 trials	6 trials in medical ICU	Intensive insulin therapy *vs.* conventional management	N/R	N/R	N/R	N/R	↓ in the surgical ICU,‡not in the others	A	
Finfer *et al.*[229]	RCT/6104 patients	Medical and surgical ICU	Intensive insulin therapy *vs.* conventional management	N/R	No difference	No difference	No difference	↑ (27.5 *vs.* 24.9%)‡	B	
Preiser *et al.*[230]	RCT/1101	Medical and surgical ICU	Intensive insulin therapy *vs.* conventional management	N/R	No difference	No difference	No difference	↑ (17.2 *vs.* 15.3%)	B	
Marik and Preiser[231]	Systematic review + meta-analysis/7 trials	Medical and surgical ICU	Impact of tight glycemic control	N/R	N/R	N/R	N/R	No difference	A	
Kansagara *et al.*[232]	Systematic review/21 trials	Medical and surgical ICU	Benefits and harms of IIT in hospitalized patients	N/R	↓ (1.484 d less) in the surgical ICU	No difference	N/R	No difference	A	
Hermans *et al.*[43]	Systematic review/2 trials	Medical and surgical ICU	IIT on incidence of CIM/CIP	↓‡	↓ (1.48 d less)‡	N/R	↓ (2 d less)‡	No difference	A	

* American Heart Association levels of evidence: A (multiple populations evaluated, data derived from multiple randomized clinical trials or meta-analyses), B (limited populations evaluated, data derived from a single randomized clinical trial or nonrandomized studies), and C (very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care). † Recommendation: I (benefits greatly surpass risks, procedure/treatment should be performed or administered), IIA (benefits surpass risks, additional focused studies needed, it is reasonable to perform procedure/treatment), IIB (benefit surpasses risks, additional studies with broad objectives needed, procedure/treatment may be considered), and III (risks surpasses benefit, procedure/treatment should not be performed. ‡ Statistically significant.

APRV = airway pressure release ventilation; ARDS = acute respiratory distress syndrome; ARISE = Australasian Resuscitation in Sepsis Evaluation; CIM = critical illness myopathy; CIP = critical illness polyneuropathy; CIPNM = critical illness polyneuropathy and myopathy; ER = emergency room; ICU = intensive care unit; IIT = intensive insulin therapy; LOS = length of stay; MRC = Medical Research Council Scale for muscle strength; N/R = not reported; PT = physical therapy; RCT = randomized controlled trial.

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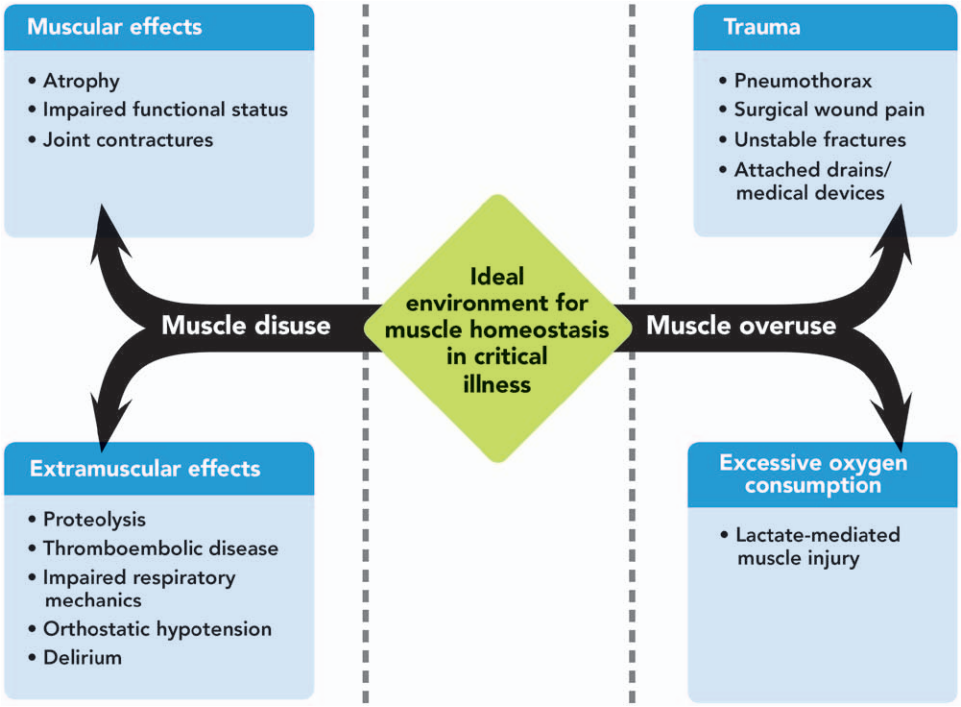

Fig. 5. Optimize drive to the skeletal muscle in the surgical intensive care unit. To provide an ideal environment for muscle homeostasis in the surgical intensive care unit, muscle activation level needs to be optimized. Muscle overuse can lead to tissue trauma and excessive oxygen consumption. Immobilization is associated with muscular and extramuscular unwarranted effects.

hospital discharge. Despite these encouraging findings, currently available evidence that physical therapy improves outcomes in the surgical ICU is of low quality.[190] Therefore, the American Thoracic Society has made strong recommendations for RCTs examining this intervention to provide strong evidence to guide healthcare professionals responsible for the care of critically ill patients who are currently underway.[36]

The ABCDE bundle is an evidence-based, multidisciplinary, multifaceted approach that seeks to reduce the risk of delirium and ICUAW by using a structured systematic approach that promotes awakening (reduce sedation), ventilator "liberation," delirium monitoring, and early mobilization.[236] This bundle promotes an interprofessional approach in the ICU that can reduce duration of ventilator dependence, hospital and ICU length of stay, incidence of ICUAW, and even mortality.[19,66]

Both excessive muscular contractions and inactivity can be associated with the morbidity of surgical ICU patients (fig. 5). Muscle homeostasis in critical illness requires a fine balance between therapeutic activity and inactivity. Muscle disuse promotes atrophy, impaired functional status, and joint contractures, as well as having extramuscular effects such as thromboembolic disease, impaired respiratory mechanics, insulin resistance, and orthostatic hypotension. Immobility associated with muscle disease increases the risk of delirium. Conversely, muscle overuse predisposes patients to traumatic sequelae including pneumothorax and surgical wound pain, as well as risk for malposition of attached drains and medical devices. Moreover, excessive oxygen consumption triggers the production of lactate, and lactic acidosis can further affect the muscle function.

Addressing Muscular Inactivation

SOMS Score. The surgical optimal mobilization score is a recently developed strategy for goal-directed early mobility after surgery that may help in conducting the needed trials.[36] It allows healthcare providers to set safe and appropriate goals for mobilizing patients, in line with their condition postoperatively. The aim is to set mobilization goals appropriate to the patient's condition early on in the postoperative period while minimizing the risk of patient harm that comes with muscle overuse (fig. 5). This may also decrease hospital costs through an efficient use of resources.[21,237,238] Currently, there are no available data to determine whether utilization of this scoring algorithm improves outcomes on the SICU, although trials are currently underway.

Keep the Diaphragm Moving. It is estimated that approximately 40% of patients in the ICU require mechanical ventilation[239] and that weaning procedures account for up to 50% of the total time spent in the ICU.[240] Controlled mechanical ventilation assumes the work of breathing from the respiratory muscles leading to the rapid development of diaphragmatic and other respiratory muscle weakness, which can occur in as little as 24 h.[1,113]

Studies on mechanical ventilation in ARDS report that spontaneous ventilation improves oxygenation parameters including Pa_{O_2} and oxygen delivery,[241,242] while also

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decreasing the global strain to the lung promoted by mechanical ventilation.[34,243,244] Spontaneous breaths during mechanical ventilation also enhance cardiac preload and improve cardiovascular parameters[208,241,245,246] and may decrease the need for paralysis and sedation.[207,247] Furthermore, protective ventilation with lower tidal volumes improves hospital outcomes including shorter ICU and hospital stay and reduces the period of mechanical ventilation[209–211] both of which can reduce the risk of ICUAW.

However, in patients with severe ARDS excessive spontaneous ventilation can increase transpulmonary pressure and lung strain. Yoshida *et al.*[248] have reported that spontaneous breathing in mice with severe ARDS led to increased lung distress because of increased work of breathing with atelectasis, higher transpulmonary pressures, and increased airway driving pressures. Patients with severe ARDS and refractory hypoxemia may actually benefit from a short period of controlled mechanical ventilation where the drive to the respiratory pump muscles is pharmacologically controlled.[41,59]

Regular Drug Review and Drug Holidays. The cost/benefit ratio of maintaining or discontinuing these medications should be tailored to the clinical course of each patient. Constant reevaluation of the need for certain medications will promote judicious use in critically ill patients. Implementing "holiday" periods in care protocols, whereby the infusions of these medications are stopped temporarily,[212,213] can decrease the duration of mechanical ventilation in surgical critically ill patients[214] and the length of stay in the ICU without increasing adverse events such as self-extubation.[212] However, it is important to bear in mind that not all patients will benefit from drug holidays; patients with increased intracranial pressure, for example, may not benefit from these drug holidays, but the sedation goal needs to be restrictively defined every day during rounds in all ICU patients.[249]

Optimize Nutrition in the ICU

Critically ill patients require nutrients in the form of either enteral or parenteral nutrition to avoid an energy deficit that contributes to lean tissue wasting.[250] It is estimated that the majority of patients in the ICU receive only 49 to 70% of calculated requirements.[220,251,252] Although it is generally agreed that excessively hypocaloric (less than or equal to recommended daily caloric intake) or hypercaloric (≥ 125%) feeding should be avoided, there is still no consensus on what the daily targets should be.[253] Higher average daily caloric energy intake is not necessarily associated with improved survival as shown in the RENAL trial,[254] which reported that the mean caloric delivery in the ICU was low, but greater levels were not associated with improved outcomes. Studies suggest that overfeeding may in fact increase rate of infections, duration of mechanical ventilation, and mortality.[162,255]

Enteral Nutrition. Enteral administration of food, fluids, and nutrients is key to maintain gut integrity, but ICU patients are often not able to feed themselves.[161] Meeting calorific requirements with enteral nutrition (EN) by means of tube feedings may improve the outcomes by preventing oxidative cell injury, attenuating the metabolic response to stress, and helping to maintain immune function.[216,256]

EN can improve outcomes compared with no supplemental nutrition in critically ill patients. In a meta-analysis of 11 studies and 837 patients, Lewis *et al.*[218] found a reduced incidence of infections and mortality, in addition to less hospitalization days in surgical and critical care patients with EN compared with patients kept "nil per mouth." Studies have reported that early EN (less than 48 h after ICU admission) in surgical and trauma patients is associated with a significant reduction in mortality,[223,257] infection rate,[215,258,259] hospital and ICU length of stay,[216,217,221,222,260] ventilator days,[217,221,222,260] and costs[258] compared with delayed EN. However, Puthucheary *et al.*[101] have shown that the catabolic state and rapid muscle wasting induced by critical illness within the first week may be independent of EN. Contrary to expectations, high protein delivery through nasogastric tube in the first week of critical illness was actually associated with greater muscle wasting,[101] thus challenging the notion that early enteral feeding is beneficial.

Interestingly, a recent RCT has demonstrated that there is no significant difference in the development of infectious complications or mortality between early enteral and parenteral feeding groups,[224] thus shedding some light on the uncertainty that exists regarding the optimal feeding route in early nutrition. The challenge lies in identifying the appropriate levels and timing of nutritional supplementation that truly improve the functional outcomes in the ICU.

Parenteral Nutrition. In patients for whom EN is not a feasible option because of the severity of their critical illness, parenteral nutrition may be considered; however, currently, the criteria and timing for initiation of parenteral nutrition are not well defined. A meta-analysis of seven RCTs involving a total of 798 patients showed that parenteral nutrition was associated with a higher rate of infection compared with no feeding.[219] Furthermore, in a multicenter randomized study of 4,640 patients admitted to the ICU, late parenteral nutrition (8 days after admission) compared with early parenteral nutrition (initiated within 48 h of admission) has been shown to reduce rates of infection, mechanical ventilation days, and healthcare costs.[162] The authors proposed that early parenteral nutrition (PN) suppressed cellular autophagic quality control impairing muscle integrity. Tolerating a macronutrient deficit for up to 1 week is believed to upregulate this quality control and decrease the risk of muscle weakness.[162] Hermans *et al.*[131] corroborated these findings in a subanalysis of the EPaNIC trial, which found that the incidence of ICUAW as assessed by the MRC score was significantly lower in the group that received late PN (34%) compared with those receiving earlier PN (43%). The late PN group also recovered faster and had higher autophagy markers on muscle biopsy compared with the early PN group. Furthermore, late initiation of parenteral nutrition

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also resulted in a mean reduction of $1,600 in healthcare costs per patient.[261]

In contrast to these studies, the Supplemental Parenteral Nutrition study found that parenteral nutrition given to patients unable to tolerate full enteral feeds on day 4 of ICU admission was associated with the reduced rates of nosocomial infections but did not improve overall mortality.[164] Another large multicenter study assessing patients with a relative contraindication to parenteral nutrition found that parenteral nutrition actually reduced the duration of mechanical ventilation, thus potentially reducing the risk of muscle weakness.[225] Thus, it remains unclear whether early parenteral nutrition is beneficial for patients who have an absolute and more prolonged contraindication to EN.[161]

In summary, there seems to be continuous controversy regarding optimal energy provision and protein intake, particularly in the early phase of critical illness.[262] Nutritional and healthcare status before ICU admission, patient's age, admission diagnosis, and disease severity all influence individual requirements, and thus, nutritional strategies and goals should be personalized to the individual patient.[233]

Glycemic Control. Tight glycemic control also plays an important role in surgical ICU outcomes. Approximately 30% of critically ill patients suffer from hyperglycemia (more than 200 mg/dl).[263] Hyperglycemia often correlates with disease severity. Stress hyperglycemia is known to be a compensatory mechanism to increase the availability of energy substrates in stressful situations such as trauma or surgical procedures. Although hyperglycemia is a physiologic response to stress, it can worsen patient outcomes. In patients with severe brain injury, for example, hyperglycemia of more than170 mg/dl is associated with longer duration of hospital stay, a worse neurologic status with higher intracranial pressures, and increased mortality.[264] Trauma patients with persistent hyperglycemia (more than 200 mg/dl) also had a significantly greater degree of morbidity and mortality, as well as infectious complications.[265] In a large RCT of 1,548 patients, strict glycemic control (blood sugar less than 110 mg/dl) was found to reduce the incidence of CIP, duration of mechanical ventilation, ICU length of stay, and mortality as well as improve functional outcomes in brain injury survivors at 1 yr.[193] Subsequent studies have not reproduced these findings and on the contrary have shown that tight glucose control can be detrimental to critically ill patients, with some studies finding an association between tight glucose control and an increased risk of hypoglycemia and mortality.[226,229–232] The NICE-SUGAR study found that tight blood glucose control (81 to 108 mg/dl) increased mortality among both medical and surgical ICU patients when compared with conventional blood glucose control (less than 180 mg/dl).[229] However, this finding may be driven by medical ICU patients, because two meta-analyses showed that the increased mortality does not occur in the SICU population.[227,228] As a result, the currently recommended target glycemic levels ranges between 110 and 180 mg/dl[229,265] to promote earlier discharge from the ICU and to decrease the incidence of ICUAW.[1]

Future Directions: Drug Targets and Gene Therapy

Potential Drug Targets. Currently, there are no approved therapeutic strategies for sarcopenia. The anabolic and catabolic signals described in the pathogenesis of disuse atrophy are appealing potential drug and gene therapy targets. Accordingly, there is currently great interest in basic science research to characterize and exploit these pathways in the quest to find a successful preventative and therapeutic agent for muscle wasting.[266] Herein, we focus on two interesting findings that have therapeutic potential.

Overexpression of a constitutively active mutant of $G\alpha i_2$ has been shown to promote myotube growth, inhibit TNF-α–induced muscle atrophy *via* transcriptional downregulation of MuRF1, enhance muscle regeneration, and stimulate a switch to oxidative fibers.[267] This suggests that both lysophosphatidic acid and/or $G\alpha i_2$ may be useful drug targets in the prevention and treatment of ICUAW.

Another approach exploits the role of mitochondria in the maintenance of muscle mass. Mitochondrial dysfunction has been shown to play an important role in disuse atrophy. PPAR Gamma Coactivator (PGC)-1α is a transcriptional coactivator with positive effects on mitochondrial biogenesis and respiration.[268] Transgenic mice overexpressing PGC-1α have demonstrated resistance to muscle wasting because the overexpression of PGC-1α prevents the activation of the AMP-activated protein kinase pathway (stimulator of muscle catabolism); the expression of MuRF1, atrogin1, and autophagic factors (implicated in muscle protein catabolism); and also muscle atrophy secondary to mechanical unloading.[269] Therefore, identifying compounds that induce and increase PGC-1α expression may be a novel and useful therapeutic strategy in the prevention of ICUAW in critically ill immobile patients.

Melanocortin-4 Receptor Antagonists. Melanocortin-4 receptor antagonism has also been shown to prevent muscle wasting in rodent models of cancer[270] and uremic/chronic kidney disease[271] cachexia making this a promising potential intervention for ICU patients who commonly have these comorbidities. Results from human clinical trials are still pending.

Myostatin Inhibitiors. Myostatin gene mutations have been associated with an increased muscle mass in humans.[175] Antagonism of myostatin enhances muscle mass and strength[272] by means of both muscle hypertrophy and hyperplasia.[273] Myostatin antibody significantly attenuated the muscle atrophy and loss of functional capacity in mice models of disuse atrophy.[274] A recently conducted phase I trial of a myostatin inhibitor in postmenopausal women proved to increase muscle mass even in these healthy subjects, with the drug seeming to be safe and well tolerated.[275]

Reversal of Neuromuscular Blockade. NMBAs are commonly used in the operating room (optimize surgical conditions) and ICU (mechanical ventilation) and can have the same effects on muscle physiology that denervation does,[63,64]

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resulting in immobilization-associated muscle atrophy, especially with long-term use. The effects of lingering NMBAs can be rapidly and safely reversed by administration of a selectively binding reversal agent, such as Sugammadex (Merck Sharp and Dohme, USA) or Calabadion (Calabash Biotech Inc., USA).[276] Currently, these agents are not licensed in the United States. A promising novel agent, Calabadion II is a broad-spectrum reversal agent that has been shown in rodents to promote faster recovery from neuromuscular blockade than Sugammadex.[276] Moreover, Calabadion II has also been shown to successfully reverse the effects of both ketamine[277] and etomidate[278] in rodents, making this drug a unique and promising development in anesthesia reversal. The clinical introduction of these drugs may limit the impact of NMBAs on the development of muscle atrophy in surgical and critically ill patients in the future.

Vitamin D Supplementation. Increased muscle strength has been reported in RCTs investigating vitamin D supplementation. In older institutionalized subjects, 6 months of vitamin D supplementation has been shown to significantly increase hip flexor and knee extensor strength by up to 25%.[279] Furthermore, vitamin D supplementation seems to benefit the weakest at baseline the most.[280] Vitamin D supplementation was also found to increase muscle fiber size[281] and improve mitochondrial function resulting in reduced muscle fatigue.[282] Further randomized controlled studies are needed to determine the clinical implications of vitamin D supplementation in critically ill patients.

ACE Inhibitors. By limiting the conversion of angiotensin I to angiotensin II, ACE inhibitors up-regulate IGF-1 levels and as a result prevent muscle wasting.[183,283] Observational studies have suggested that these findings may hold true in humans. Treatment of hypertensive subjects with an ACE inhibitor has been associated with increases in both locomotor muscle size and strength.[284,285] Moreover, in a RCT of 95 elderly subjects who had self-reported mobility difficulties but who did not have heart failure, treatment with an ACE inhibitor significantly improved 6-min walk distance compared with placebo.[286] Further studies are required to identify whether ACE inhibitors could benefit critically ill surgical patients.

Melatonin and Oxytocin. Oxytocin and melatonin have immune modulatory and antiinflammatory properties in addition to their well-known effect on regulating circadian day–night rhythms and stimulating uterine smooth muscle contraction during labor and milk ejection during lactation. In animal model of cecal ligation and puncture,[287] coadministration of oxytocin and melatonin abolished the nerve electrophysiologic alterations caused by sepsis and suppressed oxidative stress, lipid peroxidation, and TNF-α release.

Conclusion

Clinical analysis of muscle function should become a regular part of clinical examination in the ICU to allow appropriate identification and management of muscle weakness to prevent long-term morbidity and mortality and reduce healthcare costs. ICUAW weakness is a direct consequence of the patient's systemic disease and its treatment. Aggressive treatment of the underlying disease is a key strategy to its prevention. Muscular inactivity and excessive load need to be prevented, and a metabolic environment that allows for optimal recovery should be created. Future studies will demonstrate whether drugs that prevent muscular atrophy can be used to prevent ICUAW.

Search Strategy and Selection Criteria

We searched PubMed for articles in English with the term "ICU acquired weakness" in the title from January 1, 1990, to December 1, 2014. We also searched for multiple combinations of the terms "muscle weakness AND ICU," "early mobilization AND ICU," "critical illness polyneuropathy," "critical illness myopathy," "critical illness neuromyopathy," and "muscle weakness AND surgery." We also retrieved relevant articles from the reference list of key articles. Whenever possible, we prioritized the articles published in the past 5 yr but cited older references when appropriate.

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Competing Interests

Dr. Eikermann holds an equity stake in Calabash Bioscience, Inc. (Wilmington, Delaware), which develops Calabadions for biomedical applications. The other authors declare no competing interests.

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