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Acquired Neuromuscular Weakness and Early Mobilization in the Intensive Care Unit

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ABSTRACT

Survival from critical illness has improved in recent years, leading to increased attention to the sequelae of such illness. Neuromuscular weakness in the intensive care unit (ICU) is common, persistent, and has significant public health implications. The differential diagnosis of weakness in the ICU is extensive and includes critical illness neuromyopathy. Prolonged immobility and bedrest lead to catabolism and muscle atrophy, and are associated with critical illness neuromyopathy and ICU-acquired weakness. Early mobilization therapy has been advocated as a mechanism to prevent ICU-acquired weakness. Early mobilization is safe and feasible in most ICU patients, and improves outcomes. Implementation of early mobilization therapy requires changes in ICU culture, including decreased sedation and bedrest. Various technologies exist to increase compliance with early mobilization programs. Drugs targeting muscle pathways to decrease atrophy and muscle-wasting are in development. Additional research on early mobilization in the ICU is needed.

MEDICINE has long turned to bedrest as an adjunct in the treatment of severe illness and convalescence after surgery. Hippocrates suggested that all pain is relieved by bedrest.[1] However, in the early 20th century, physicians and researchers began to recognize the "evil sequelae of complete bedrest,"[2] noting that "prolonged periods of recumbency in bed are anatomically, physiologically, and psychologically unsound and unscientific."[3] More recently, a systematic review of 39 trials of bedrest for 15 different conditions showed no benefit and highlighted the potential for harm,[1] including atelectasis, venous thrombosis, pulmonary edema, bone atrophy, muscle-wasting, vasomotor instability, constipation, and backache.[2,3]

Traditionally, healthcare providers working in intensive care units (ICUs) have focused their attention on normalizing the severe cardiopulmonary derangements that put their patients' lives at risk. However, as survival from critical illness has improved, focus has shifted to include preventing the sequelae of critical illness, including neuromuscular weakness. Neuromuscular weakness occurs in approximately 25–50% of critically ill patients,[4,5] and persists for years after ICU discharge, such that only half of survivors return to work within a year.[6,7] Early mobilization of ICU patients has been touted as one intervention to decrease the weakness and deconditioning associated with critical illness. Recent studies have demonstrated that early mobilization is safe, feasible, and beneficial in the ICU population.[8–11]

This review outlines the physiologic consequences of bedrest; the pathophysiology of neuromuscular weakness acquired in the ICU; and the safety, feasibility, and potential benefits of early mobilization during critical illness.

The Physiologic Consequences of Bedrest

It has been said that rest "of injured parts and of diseased bodies is the most valuable of all methods of treatment but may lead to untoward results when utilized either injudiciously or excessively."[12] Indeed, in recent years, the medical community has increasingly acknowledged the adverse effects of physical inactivity, bedrest, and immobility.

During bedrest, skeletal muscle utilization is decreased. Muscles are activated less frequently, for shorter periods of time, and are responsible for smaller loads. This mechanical unloading of muscles triggers a cascade of responses – slowed protein synthesis, accelerated proteolysis, and increased apoptosis – that alters skeletal muscle morphology, the

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Table 1. Mnemonic for Differential Diagnosis of Generalized Weakness in the ICU

M	Medications: steroids, neuromuscular blockers (pancuronium, vecuronium), zidovudine, amiodarone
U	Undiagnosed neuromuscular disorder: myasthenia, LEMS, inflammatory myopathies, mitochondrial myopathy, acid maltase deficiency
S	Spinal cord disease (ischemia, compression, trauma, vasculitis, demyelination)
C	Critical illness myopathy, polyneuropathy
L	Loss of muscle mass (cachectic myopathy, rhabdomyolysis)
E	Electrolyte disorders (hypokalemia, hypophosphatemia, hypermagnesemia)
S	Systemic illness (porphyria, AIDS, vasculitis, paraneoplastic, toxic)

Reprinted with permission from Maramattom *et al.* and Wolters Kluwer Health.[19]

AIDS = acquired immunodeficiency syndrome; ICU = intensive care unit; LEMS = Lambert–Eaton myasthenic syndrome.

proportion of slow and fast twitch muscle fibers, contractility, and aerobic capacity, ultimately resulting in catabolism, atrophy, and weakness.[13,14]

Paddon-Jones *et al.* evaluated the effect of 28 days of bedrest on protein loss in young, healthy volunteers and found a 23% reduction in leg-extension strength.[15] Concomitant inflammation and stress exacerbate the weakness associated with bedrest. In a follow-up study, Paddon-Jones *et al.* administered hydrocortisone to achieve plasma cortisol levels consistent with acute illness in volunteers subjected to 28 days of bedrest and found a 28% loss of leg-extension strength and a 3-fold greater loss of lean leg mass compared with bedrest alone ($P = 0.004$).[16]

A recent systematic review of 39 trials of bedrest (n = 5,777) for 15 different conditions evaluating a variety of outcomes including disability, pain, and mortality found no significant improvement in outcomes for any condition. In nine conditions, including acute myocardial infarction, low back pain, hepatitis, and pregnancy-induced hypertension, bedrest was associated with worsened outcomes.[1]

ICU-acquired Weakness

Neuromuscular weakness in the ICU is common; approximately 50% of ICU patients with sepsis, multiorgan failure, or prolonged mechanical ventilation have electrophysiologic evidence of neuromuscular dysfunction.[5] The incidence increases to 100% in patients with both systemic inflammatory response syndrome/sepsis and multiorgan failure.[17] More than 25% of ICU patients undergoing mechanical ventilation for 7 or more days have clinical evidence of weakness on awakening.[4] Marked diaphragmatic atrophy can be seen 18 h after the onset of mechanical ventilation,[18] and the onset of weakness may occur as early as ICU day 2.[17]

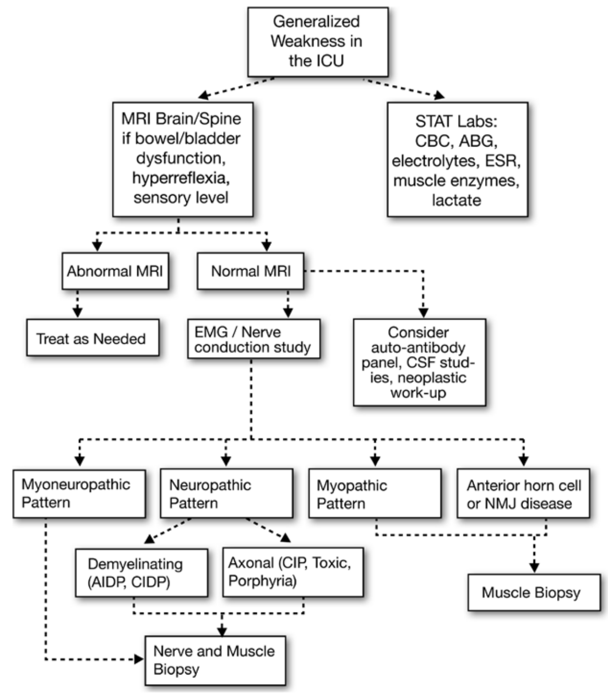

Fig. 1. Algorithm for evaluation of generalized weakness in the ICU. Adapted with permission from Maramattom *et al.* and Wolters Kluwer Health.[19] ABG = arterial blood gas; AIDP = acute inflammatory demyelinating polyneuropathy; CBC = complete blood count; CIDP = chronic inflammatory demyelinating polyneuropathy; CIP = critical illness polyneuropathy; CSF = cerebrospinal fluid; EMG = electromyography; ESR = erythrocyte sedimentation rate; ICU = intensive care unit; MRI = magnetic resonance imaging; NMJ = neuromuscular junction; STAT = *statim*.

The differential diagnosis for neuromuscular weakness in the ICU is broad, and the mnemonic MUSCLES aids clinicians in remembering some of the most common causes (table 1).[19] A clinical algorithm for the evaluation of generalized weakness in the ICU, which includes laboratory testing, radiographic imaging, and electromyography, can also be helpful (fig. 1).

Included in the long differential of weakness in the ICU is critical illness neuromyopathy (CINM). CINM is an umbrella term for a spectrum of neuromuscular disorders associated with critical illness, including critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and disorders of the neuromuscular junction.[5,19] Differentiating between CIP and CIM often requires electrophysiology and/or direct muscle stimulation; although compound muscle action potential amplitudes are reduced in both conditions, sensory nerve action potential amplitudes are reduced or absent in CIP but normal in CIM (fig. 2).[20] In addition, creatine kinase levels are increased in about 50% of CIM patients, but normal in those with CIP. CIM can be further divided into four histologic subtypes: necrotizing, cachectic, acute rhabdomyolysis, and thick filament loss. The necrotizing subtype is associated with a poorer prognosis.[19] Because CIP and CIM frequently occur concurrently, they are often

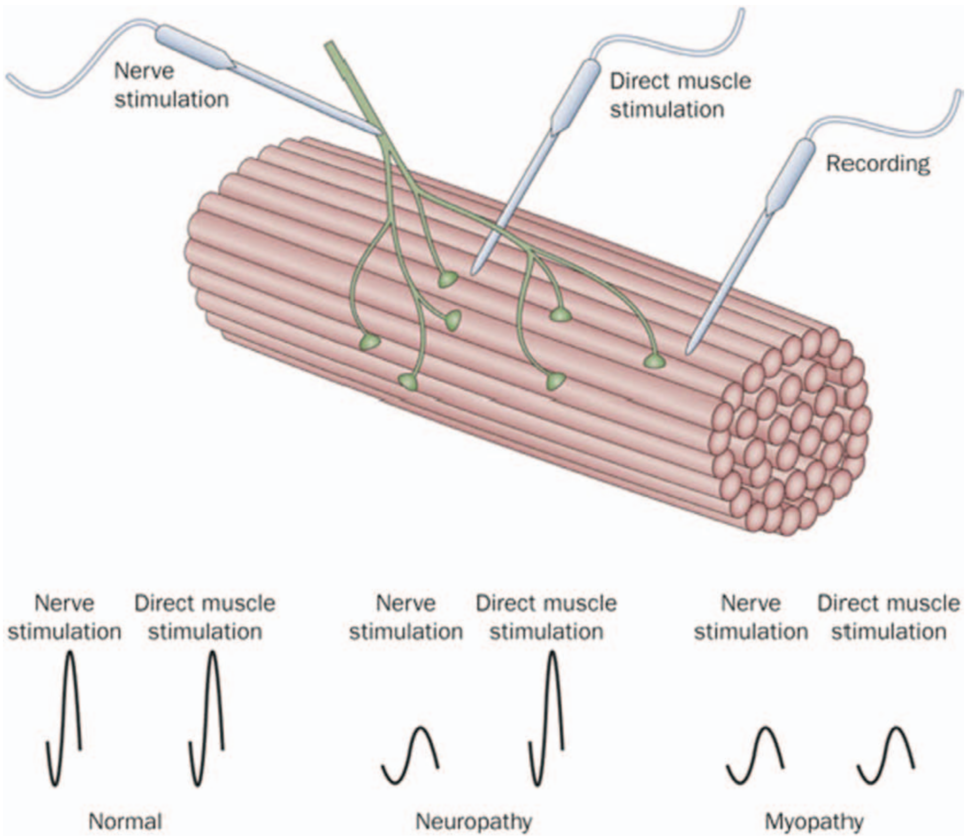

Fig. 2. Direct muscle stimulation, during which stimulating and recording electrodes are both placed in the muscle. In critical illness neuropathy, compound muscle action potentials are reduced or absent after conventional nerve stimulation but normal after direct muscle stimulation. In critical illness myopathy, compound muscle action potentials are reduced or absent after both conventional nerve stimulation and direct muscle stimulation. Reproduced with permission from Zink *et al.* and Macmillan Publishers Ltd: Nature Review Neurology, 2009.[20]

treated as one entity: CINM. The pathophysiology of CINM is complex and includes the sequelae of bedrest, the effects of critical illness-induced cytokine production, and possibly the interplay of drugs such as neuromuscular blockers and corticosteroids (fig. 3). Protein-energy malnutrition, electrolyte imbalances, and glutamine deficiency also play a role, highlighting the importance of nutritional supplementation in the critically ill.[21,22]

ICU-acquired weakness (ICUAW), defined as bilateral symmetrical limb weakness, is the clinical manifestation of CINM.[14] The typical presentation is flaccid quadriparesis and hyporeflexia or areflexia, with sparing of the cranial nerves.[19] This acquired weakness is associated with respiratory muscle weakness, difficulty weaning from the ventilator, and prolonged ICU length of stay (LOS).[14,23] A prospective cohort study of 174 ICU patients in five academic medical centers requiring at least 5 days of mechanical ventilation without evidence of preexisiting neuromuscular disease revealed that ICUAW was independently associated with hospital mortality in both a multivariate logistic regression model (odds ratio OR: 7.8, 95% CI: 2.4–25.3) and in an analysis using propensity score matching (OR: 5.2, 95% CI: 1.5–18.3).[24]

Several studies have evaluated the risk factors for CINM and ICUAW (table 2). The systemic inflammatory response syndrome, sepsis, and multiorgan failure have been repeatedly implicated. A systematic review of neuromuscular dysfunction acquired in critical illness included 1,421 ICU patients in 24 studies and identified hyperglycemia, the systemic inflammatory response syndrome, sepsis, multiorgan dysfunction, renal replacement therapy, and catecholamine administration as risk factors for the development of CINM. No consistent relationship between CINM and age, gender, severity of illness, or exposure to corticosteroids or neuromuscular blocking agents was found.[5] In a prospective cohort study of 95 ICU patients who underwent mechanical ventilation for 7 days or more in four hospitals in France, De Jonghe *et al.* found that the independent predictors of ICUAW were female sex (OR: 4.66, 95% CI: 1.19–18.30), the number of days with dysfunction of two or more organs (OR: 1.28, 95% CI: 1.11 to 1.49), duration of mechanical ventilation (OR: 1.10, 95% CI: 1.00 to 1.22), and administration of corticosteroids (OR: 14.90, 95% CI: 3.20–69.80).[4] Although corticosteroids inhibit protein synthesis in type II muscle fibers and contribute to severe protein catabolism,[25] the relationship between corticosteroids and

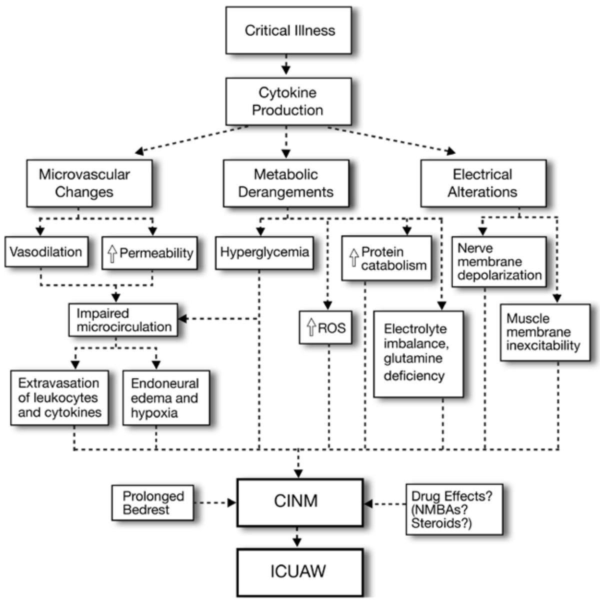

Fig. 3. Pathophysiology of CINM/ICUAW. Adapted with permission from Hermans *et al.* and John Wiley and Sons.[21] CINM = critical illness neuromyopathy; ICU = intensive care unit; ICUAW = ICU-acquired weakness; NMBA = neuromuscular blocking agent; ROS = reactive oxygen species.

CINM/ICUAW has been inconsistent, and corticosteroids were even found to be protective for the development of weakness in one study.[26] Whether the use of neuromuscular blocking agents increases the risk of CINM and ICUAW remains controversial; a dose-dependent response has been reported in patients with severe asthma requiring mechanical ventilation,[27] but this relationship has not borne out in the general adult ICU population.[4,5,28]

Investigations of potential interventions to prevent CINM/ICUAW are relatively sparse. A recent Cochrane review identified only one successful intervention: intensive insulin therapy.[21] Unfortunately, despite its protective effect on the development of CINM/ICUAW, intensive insulin therapy may increase mortality in critically ill patients.[29] Because prolonged immobilization and bedrest have been shown to accelerate muscle loss and exacerbate ICUAW, mobility therapy has emerged as a potential preventative measure.[15,16,23]

Table 2. Risk Factors Implicated in the Development of ICU-acquired Weakness

SIRS/sepsis
Multiorgan failure
Hyperglycemia
Renal replacement therapy
Catecholamine administration
Female sex
Duration of mechanical ventilation
Corticosteroids
Neuromuscular blocking agents

ICU = intensive care unit; SIRS = systemic inflammatory response syndrome.

As survival from critical illness improves, and with preventative measures lacking, CINM and ICUAW present a grave public health problem. Herridge *et al.* studied long-term outcomes of 109 survivors of acute respiratory distress syndrome from four Canadian hospitals and found significant morbidity.[6] The patients tended to be young (median age, 45 y) and critically ill (median Acute Physiology, Age, and Chronic Health Evaluation APACHE II score, 23), and had prolonged mechanical ventilation (median duration, 21 days), ICU LOS (median duration, 25 days), and hospital LOS (median duration, 48 days). Lung function improved significantly during the first year after ICU discharge, with normalization of lung volumes and spirometry by 6 months, and improvement in carbon monoxide diffusion capacity to 72% predicted at 12 months. However, "all patients reported poor function and attributed this to the loss of muscle bulk, proximal weakness, and fatigue."[6] One year after ICU discharge, the median distance walked in 6 min was 66% of predicted. In a multivariate analysis of functional status (as determined by distance walked in 6 min), the use of any systemic corticosteroid was the strongest predictor at 3 months. At 6 months, rapid resolution of lung injury and multiorgan dysfunction and absence of ICU-acquired illnesses became the most important determinants, whereas corticosteroid use was no longer statistically significant. Interestingly, at 12 months, none of the variables remained statistically significant, and the model did a poor job of explaining continued poor functional status (*R2* = 0.10). Nonetheless, only 49% of survivors had returned to work 1 yr after ICU discharge.

At 5 yr after ICU discharge, all patients reported subjective weakness and decreased exercise capacity compared with before ICU admission.[7] Although there was no evidence of clinical weakness on examination, the median distance walked in 6 min remained lower than expected based on age and sex (436 m, 76% predicted). Although 77% of patients had returned to work, patients often required a modified work schedule, gradual transition back to work, or job retraining. In addition, patients were plagued with the psychologic ramifications of their severe illness, with more than half of survivors experiencing at least one episode of physician-confirmed depression or anxiety. Furthermore, the utilization of health care was high, with average costs of $5,000–6,000 per patient per year after ICU discharge, significantly more than costs incurred by healthy workers.

Iwashyna *et al.* studied long-term functional disability and cognitive impairment among survivors of severe sepsis.[30] This prospective cohort study included 516 severe sepsis survivors and a control group of 4,517 survivors of a non-sepsis hospitalization, all drawn from the Health and Retirement study. The definition of severe sepsis was claims-based, requiring both an infection and new-onset organ dysfunction during a single hospitalization. All patients were older than

50 yr old, and the mean age of severe sepsis survivors was 76.9 yr. Functional status and cognitive status were assessed *via* survey before and after the hospitalization, with follow-up for up to 7.8 yr before hospitalization and 8.3 yr afterward. The survey assessed ability to independently complete activities of daily living and instrumental activities of daily living in order to determine functional status, and relied on tests of memory, serial seven subtractions, and naming in order to detect cognitive impairment. Among patients with no functional limitations at baseline, severe sepsis was associated with the development of 1.57 new limitations (95% CI: 0.99–2.15), as well as a more rapid rate of development of functional limitations after hospitalization (0.51 new limitations per year, $P = 0.007$ compared with baseline). The study also found that the incidence of severe sepsis was highly associated with progression to moderate to severe cognitive impairment (OR: 3.34, 95% CI: 1.53–7.25), perhaps because of the effects of sepsis-induced inflammation and hypoperfusion on the brain. The effects of severe sepsis were similar regardless of the need for mechanical ventilation. Remarkably, the declines in physical function and cognitive function persisted for at least 8 yr.

Early Mobilization

Safety and Feasibility in Medical Patients

Given the prolonged morbidity and cost associated with CINM and ICUAW, identification and implementation of prevention strategies is of utmost importance. Among suggested prevention strategies is early physical therapy and mobilization of ICU patients. Despite longstanding knowledge of the evils of bedrest and the benefits of physical activity, early mobilization in the ICU did not emerge as a popular therapy until relatively recently.[2,3,12]

There are many perceived barriers to mobilization. First, ICU patients, perhaps by definition, have severe derangements in physiologic equilibrium, causing healthcare providers to focus their attention on treatment of the organ systems that most threaten survival. Because of the gravity of their illnesses, critically ill patients are often deemed "too sick" to engage in physical activity, especially early in their ICU course.[9] Furthermore, the use of sedation is often seen as a barrier to physical therapy as patients are often too somnolent to participate. In addition, ICU patients often have many indwelling lines and tubes, including endotracheal tubes, central venous catheters, arterial lines, bladder catheters, even left ventricular assist devices and extracorporeal membrane oxygenator (ECMO) cannulae, and the risk of dislodging this equipment increases with patient movement.[31] The use of vasopressors and continuous renal replacement therapy have also been identified as barriers. Finally, ICU delirium may limit patient participation in therapy sessions.[32]

In order to address whether these perceived barriers preclude early mobilization in the ICU, several studies have attempted to assess the safety and feasibility of physical activity in the critically ill (table 3).[8,9,33] Bailey *et al.* performed a prospective cohort study of early activity in respiratory failure patients in an eight-bed respiratory ICU (RICU).[9] The study included 103 RICU patients who required mechanical ventilation for more than 4 days. *A priori* inclusion criteria were ability to respond to verbal stimulus, fraction of inspired oxygen (FIO_2) 0.60 or less, positive end-expiratory pressure 10 cm H_2O or less, and absence of orthostatic hypotension and catecholamine infusions. Patients who did not fully meet these criteria, however, were included if they were deemed otherwise ready for activity. Ninety-four percent of patients had been admitted to another ICU before transfer to the RICU, with a mean time to RICU admission of 10.5 ± 9.9 days. The most common diagnosis was sepsis (41% of patients). Mean APACHE II score on admission to the RICU was 17 ± 4.8. Early activity was defined as starting at physiologic stabilization; activity events included sitting on the edge of the hospital bed without back support, sitting in a chair after transfer from bed, and ambulating, with the ultimate goal being to ambulate more than 100 feet before ICU discharge. Feasibility and safety were assessed *via* six predefined activity-related adverse events (fall to knees, tube removal, systolic blood pressure more than 200 or less than 90 mmHg, oxygen saturation less than 80%, and extubation). During 1,449 activity events, the incidence of adverse events was less than 1%, and there were no extubations. Sixty-nine percent of patients were able to ambulate more than 100 feet before RICU discharge. Thus, the authors concluded early activity to be safe and feasible in RICU patients.[9]

Of course, one criticism of the study by Bailey *et al.* is that patients admitted to a RICU are likely to be less severely ill (as evidenced by the relatively low APACHE II score on RICU admission), and that "early" activity in the RICU is, in fact, not early at all when the time to RICU admission is more than 10 days. More recently, Bourdin *et al.* completed a prospective observational study on the feasibility of early physical activity in the medical ICU at a single center.[33] Twenty consecutive ICU patients with ICU LOS of 7 days or more and duration of mechanical ventilation of 2 days or more were included in a rehabilitation program that included chair-sitting, tilting up, and walking. Median age was 68 (interquartile range IQR: 32–85), and Simplified Acute Physiology 2 score 42 (IQR: 22–75), predicting a mortality rate of 28%. The most common primary admitting diagnosis was acute respiratory failure (75%), and 55% of patients had chronic respiratory disease. Activity sessions were performed daily unless the patient met predefined exclusion criteria, including altered mental status (agitation, confusion), shock (systolic blood pressure less than 90 mmHg or vasopressor requirement), respiratory failure (respiratory rate more than 35 breaths/min, Pao_2 to FIO_2 ratio less than 200, $Paco_2$ more than 50 mmHg, or pH less than 7.30), ongoing renal replacement therapy, and intravenous sedation. Contraindications were present on 43% of days. Thirty-three percent of interventions were done during

Table 3. Evidence for Early Mobilization in the ICU: Safety and Feasibility

Study	Design	Patient Population	Intervention	Primary Endpoint	Major Findings
Bailey *et al.*[9]	Prospective cohort study	103 respiratory ICU patients at a single center requiring mechanical ventilation for more than 4 days.	Activity therapy (sitting on bed, sitting in chair, and ambulating)	Activity-related adverse event (fall to knees, tube removal, systolic blood pressure more than 200 or less than 90 mmHg, oxygen saturation less than 80%, extubation)	1,449 activity events were conducted. Incidence of adverse events was less than 1%, with no extubations.
Bourdin *et al.*[33]	Prospective observational study	20 medical ICU patients at a single center with ICU LOS 7 days or more, requiring mechanical ventilation for 2 days or more	Rehabilitation program (chair-sitting, tilting-up, and walking)	Exercise-induced changes in vital signs and adverse events (drop in muscle tone, oxygen saturation less than 88% for more than 1 min, unscheduled extubation, systolic blood pressure less than 80 mmHg while standing)	There were 424 activity sessions, with 33% during mechanical ventilation. Incidence of adverse events was 3%, with one unscheduled extubation.
Pohlman *et al.*[8]	Descriptive study of intervention arm of randomized controlled trial on early PT/OT	49 sedated patients in the medical ICU at two centers who had been on mechanical ventilation for less than 72 h and were expected to continue for at least another 24 h	Early exercise and mobilization (starting with active assisted range of motion exercises and progressing to bed mobility exercises, activities of daily living, transferring, and ambulating) during periods of daily sedation interruption	N/A	PT/OT took place on 87% of days. One or more barriers to mobilization (acute lung injury, vasoactive medication administration, delirium, renal replacement therapy, of body mass index 30 or more kg/m^2) were present in 89% of sessions. Adverse events (MAP less than 65, HR less than 40 or more than 130, pulse oximetry less than 88%, ventilator dysynchrony, patient distress, new arrhythmia, concern for myocardial ischemia or airway device integrity, fall to knees, extubation) occurred in 16% of sessions and required cessation of therapy in 4% of sessions, with no extubations.
Turner *et al.*[38]	Case series	3 patients (ages 16, 20, 24) with end-stage respiratory failure on ECMO awaiting lung transplantation	Active rehabilitation, physical therapy, and ambulation	N/A	Patients were safely rehabilitated on ECMO. Following lung transplant, all patients were liberated from mechanical ventilation, ambulatory, and transferred out of the ICU in less than 1 week.
Garzon-Serrano *et al.*[34]	Prospective observational study	63 patients consecutively admitted to the surgical ICU at a single center	Mobilization therapy performed by nurses daily and by physical therapists when ordered by the ICU physician. Mobilization level was scored by provider performing therapy, from 0 to 4. (Phase 0, not mobilized because of contraindication; phase 1, passive range of motion and sitting in bed; phase 2, sitting on site of bed or transferring to chair *via* mechanical lift; phase 3, standing; phase 4, ambulating)	Mobilization level achieved by nurses *vs.* physical therapists	232 assessments performed, 179 included in final analysis. Physical therapists achieved a higher level of mobilization than nurses (mean mobilization level 2.3 *vs.* 1.2, $P <$ 0.0001). There were no adverse events.

ECMO = extracorporeal membrane oxygenation; HR = heart rate; ICU = intensive care unit; LOS = length of stay; MAP = mean arterial pressure; N/A = not applicable; PT/OT = physical therapy/occupational therapy.

mechanical ventilation. Walking was achieved during 11% of activity sessions. The incidence of adverse events was 3%, including one unscheduled extubation.[33]

Pohlman *et al.* published a descriptive study of early physical and occupational therapy (PT/OT) in 49 mechanically ventilated medical ICU patients at two tertiary care academic centers.[8] In this cohort, the median age was 57.7 yr (IQR: 36.3–69.1) and median APACHE II score 20 (IQR: 15.8–24). The most common primary admitting diagnosis was acute lung injury (55%), and 57% of patients were in septic shock. Patients were assessed daily for appropriateness of physical and occupational therapy intervention; PT/OT screen was coupled with daily sedation interruption. Patients passed the screen and were deemed eligible for PT/OT if they did not have any of the following contraindications: mean arterial pressure less than 65 mmHg, heart rate less than 40 or more than 130 beats/min, respiratory rate less than 5 or more than 40 breaths/min, pulse oximetry less than 88%, evidence of increased intracranial pressure, active gastrointestinal blood loss, active myocardial ischemia, undergoing a procedure, severe agitation, or insecure airway. The median time from intubation to initiation of therapy was 1.5 days (IQR: 1.0–2.1). PT/OT took place on 87% of total days, with ambulation occurring in 15% of sessions. One or more barriers to mobilization – acute lung injury, vasoactive medication administration, delirium, renal replacement therapy, or body mass index 30 kg/m^2 or more – were present in 89% of sessions. Notably, FIO_2 was 60% or more during 35% of sessions on mechanical ventilation, vasoactive drugs were infusing during 17% of sessions (with two or more pressors infusing during 14% of sessions), and continuous renal replacement therapy occurred during 9% of sessions. Delirium was present in 53% of sessions and may have restricted patients from participating in higher-level activities such as ambulation.[32] Minor adverse events were reported during 16% of sessions, including oxygen desaturation, increased heart rate, ventilator dysynchrony, and agitation, but required premature cessation of therapy in only 4% of sessions. No unplanned extubations occurred.[8]

Thus, early mobilization is feasible and appears to be safe in most medical ICU patients. Of course, the true safety of this intervention will only be understood when the practice of early mobilization has become widespread, and the number of patients engaging in activity is large enough to ascertain the incidence of rare but potentially catastrophic adverse events.

Safety and Feasibility in Surgical Patients

Surgical patients have unique considerations, including wound healing, pain, recent musculoskeletal trauma, weight-bearing restrictions, and surgical drains. Literature on early mobilization in the surgical ICU is limited. Garzon-Serrano *et al.* performed a prospective observational study of early mobilization in the surgical ICU of a tertiary care academic center.[34] Although the goal of the study was to compare the level of mobilization achieved in nurse-led *versus* physical therapist-led activity sessions, the study provides some insight into the safety and feasibility of early mobilization in surgical patients. Sixty-three consecutive patients admitted to the surgical ICU were enrolled. The majority (64%) of patients were admitted after major surgery, including abdominal aortic aneurysm repair, pancreatectomy, esophagectomy, and tracheal resection. Specific exclusion criteria were not specified in order to "avoid unwarranted limitation or withholding of mobility interventions"; however, inability to maintain adequate arterial blood pressure or target oxygen saturation were both considered contraindications. Patients were progressively mobilized, starting with passive range of motion in bed and progressing to sitting on the side of the bed, transferring to a chair, standing, and ambulating. A total of 179 mobilization therapy sessions were completed, beginning as early as surgical ICU day 1. Although physical therapists reported higher levels of mobilization than nurses, approximately 10% of nurse-led mobilization sessions included ambulation. No adverse events were reported.

Additional data on the safety and feasibility of early mobilization in the surgical ICU comes from the burgeoning literature on the intervention in the left ventricular assist device and ECMO populations. Indeed, a number of case reports have shown anecdotal evidence that physical therapy and mobilization can be safe even in patients with cardiac cachexia requiring left ventricular assist device implantation,[35] as well as patients requiring ECMO as a bridge to lung transplantation.[36-38] At our institution, we routinely mobilize ICU patients regardless of intubation status or ECMO requirement.

How or whether to mobilize patients in the trauma ICU is a more difficult question, as the data on this population is lacking, and such patients suffer from injuries that may limit or preclude mobilization. The literature on rehabilitation of patients not in the ICU after operative repair of traumatic hip fractures reveals that although early mobilization is seen as a priority,[39] these patients often suffer from orthostatic intolerance, putting them at increased risk of fainting, falls, and damage to prostheses.[40] How this translates to an ICU patient with polytrauma is unknown. In a recent review citing the safety and benefits of early mobilization in medical ICU patients, Banerjee *et al.* endorse early mobilization in the trauma ICU without providing specific recommendations on patient selection or treatment plan.[41] Similarly, Markandaya *et al.* recently published a treatment plan for patients with acute spinal cord injury, in which they recommended "early mobilization (with spinal column stability ensured by operative fixation, external braces, or both), including frequent turning, out-of-bed to chair, and passive range of motion of the limbs,"[42] even though there have been no studies of the intervention in this population.

Outcomes

Several studies have assessed the impact of early mobilization in the ICU on various outcome measures. One early study assessed whether passive stretching can decrease muscle-wasting in critically ill patients.[43] Five patients requiring neuromuscular blockade were enrolled. Each patient served as his or her own control: One leg of each patient received continuous passive motion, although the other leg received standard care. Although the amount of muscle-wasting was similar between limbs, there was decreased muscle fiber atrophy and protein loss in the limb receiving continuous passive motion, suggesting that passive stretching preserves muscle architecture.

In a retrospective analysis of 49 patients admitted to a ventilatory rehabilitation unit, all of whom were bedridden and had clinical evidence of severe weakness on admission, Martin *et al.* found that immediate initiation of a whole-body rehabilitation program was associated with increases in upper and lower extremity strength.[44] Furthermore, upper extremity strength on admission inversely correlated with time to wean from the ventilator ($R^2 = 0.54$, $P < 0.001$). Eligibility criteria included respiratory and nonrespiratory medical stability, including tracheostomy for invasive ventilation, manageable secretions, FIO_2 less than 50%, positive end-expiratory pressure less than 5 cm H_2O, peripheral oxygen saturation more than 92%, stable ventilator settings, no dyspnea, controlled sepsis, no uncontrolled hemorrhage, no uncontrolled arrhythmias or heart failure, and no coma. Of note, this study was limited by its retrospective nature and lack of a control group.

Needham *et al.* performed a prospective before/after quality-improvement study including 57 patients in a single medical ICU.[45] The project involved creation of a multidisciplinary team; hiring of one full-time physical therapist, one full-time occupational therapist, and one part-time rehabilitation assistant; establishing guidelines for eligibility for early mobilization and PT/OT consultation; encouraging administration of sedating medications on an as-needed basis in lieu of continuous infusions; changing the standard ICU admission orders' default activity level from "bed rest" to "as tolerated"; and increasing consultations to physiatry and neurology. Patients were considered eligible if they were not comatose, required only moderate respiratory support (defined as positive end-expiratory pressure of 10 or less and FIO_2 of 60% or less), and had no increase in vasopressor requirements for at least 2 h before therapy. Although limited by its before/after design, this study did show that, after implementation of the intervention, the median number of rehabilitation treatments per patient increased (1 *vs.* 7, $P < 0.002$), whereas ICU and hospital LOS decreased (by 2.1 day 95% CI: 0.4–3.8) and 3.1 day 95% CI: 0.3–5.9, respectively).

Morris *et al.* performed the first study assessing the efficacy, cost, and benefits of early mobilization in the ICU.[10] This prospective cohort study included 330 medical ICU patients with acute respiratory failure requiring mechanical ventilation. Exclusion criteria were extensive, including inability to walk without assistance before acute illness, nonverbal status at baseline, preadmission immunocompromised state, preexisting neuromuscular disease, acute stroke, body mass index more than 45 kg/m^2, hip fracture, unstable cervical spine or pathologic fracture, mechanical ventilation more than 48 h before transfer from an outside facility, current hospitalization more than 72 h, cardiopulmonary resuscitation at admission, do not resuscitate order at admission, hospitalization within 30 days of admission, therapy for cancer within 6 months of admission, and readmission to the ICU. Patients were assigned to a protocol of activity therapy within 48 h of mechanical ventilation or usual care *via* block allocation. There were no differences in baseline characteristics between groups; mean APACHE II scores were 21.6 and 23.5 in the usual care group and protocol group, respectively ($P = 0.092$). Furthermore, there was no difference in the number of patients with perceived barriers to mobility (*e.g.*, arterial catheters, central venous catheters, neuromuscular blocking agents) between the two groups. The study found that the protocol patients were out of bed earlier (5 *vs.* 11 days, *P* ltequ 0.001) and had shorter ICU and hospital LOS (5.5 *vs.* 6.9 days, $P = 0.025$ and 11.2 *vs.* 14.5 days, $P = 0.006$, respectively). There was no difference in cost between the two groups. A follow-up study assessed the mortality and hospital readmission status of the 280 patients in the original cohort who survived to hospital discharge.[46] Forty-seven percent were readmitted or died within the first year after discharge. Multivariate logistic regression was used to identify variables from the index hospitalization that predicted hospital readmission or death within 12 months of hospital discharge. Lack of early mobilization in the ICU was one of four predictors identified (OR: 1.77, 95% CI: 1.04–3.01).

Additional studies, including two randomized controlled trials, have corroborated the benefit of early mobilization on ICU outcomes.[11,45,47,48] In a randomized controlled trial of 90 medical and surgical ICU patients, Burtin *et al.* compared respiratory physiotherapy, daily standardized mobility sessions of the limbs, and 20 min per day of bedside ergometry with respiratory physiotherapy and daily standardized mobility sessions of the limbs alone.[48] Patients were included only after ICU day 5, if they had expected ICU course of at least another 7 days. Exclusion criteria were as follows: leg, pelvis, or lumbar spine trauma or surgery; body mass index more than 35 kg/m^2; open abdomen; serious bedsore or ulcers; body length less than 1.5 meters; preexisting neuromuscular weakness; acute stroke; status epilepticus; intracranial pressure more than 20 mmHg; coagulation abnormalities; severe agitation or psychiatric disease; cardiopulmonary instability (defined as FIO_2 more than 55%, $Paco_2$ less than 65 torr, minute ventilation more than 150 ml/kg, respiratory rate more than 30, need for significant vasopressor support); and anticipated fatal outcome. Despite randomization, the treatment group had a significantly longer ICU stay before inclusion as compared with the control group (mean 14 days *vs.* 10 days, $P < 0.05$), a longer period of intravenous sedation (median 11 days *vs.* 8 days, $P < 0.05$), and a larger total dose of neuromuscular blocking agents (150 mg *vs.* 75 mg, $P < 0.05$). Other baseline characteristics were similar between the two groups, with mean APACHE II score on admission 25 ± 4 in the control group and 26 ± 6 in the intervention group. At hospital discharge, 6-min walk distance was greater in the treatment group (29 *vs.* 25% predicted, $P < 0.05$), and there was a trend toward increased discharge to home in this group (74% *vs.* 66%, $P > 0.05$). Furthermore, patients in the treatment group reported a significantly higher feeling of subjective well-being. Weaning time, ICU LOS, and hospital LOS were similar in the two groups.

Schweickert *et al.* randomized 104 sedated ICU patients who had been on mechanical ventilation for less than 72 h and were expected to continue for at least another 24 h to early PT/OT during daily sedation interruptions or daily sedation interruption with activity as ordered by the primary team.[11] Patients were excluded if they had rapidly progressive neuromuscular disease, cardiopulmonary arrest, 6-month mortality estimated to be more than 50%, increased intracranial pressure, or absent limbs. Baseline characteristics were similar between the two groups; median APACHE II score was 20.0 (IQR: 15.8–24.0) in the intervention group and 19.0 (IQR: 13.3–23.0) in the control group. The most common primary diagnosis in both groups was acute lung injury. The primary outcome, return to independent functional status at hospital discharge, was observed in 59% of patients in the early activity group as compared with 35% of patients in the control group (P = 0.02). Patients receiving the intervention also experienced less delirium (2.0 *vs.* 4.0 days with delirium, $P = 0.03$) and more ventilator free days (3.4 *vs.* 6.1, $P = 0.02$). There was a trend toward increased discharge to home in the intervention group (43% *vs.* 24% patients discharged to home, P = 0.06). There was no difference in the incidence of ICU-acquired paresis at hospital discharge (31% *vs.* 49%, P = 0.09), although the study was not powered to detect this outcome. ICU LOS, hospital LOS, and hospital mortality were similar in the two groups.

Based on the mounting evidence of the complications of prolonged immobility and the potential benefits of early activity in the critically ill, the European Respiratory Society and European Society of Intensive Care Medicine created a task force on physiotherapy for critically ill patients.[49] This task force was convened before the publication of data from the randomized controlled trials of early mobilization; thus, most recommendations were levels C and D. They recommended that "mobilization and muscle training should be instituted early," but noted that patients with hemodynamic instability or poor respiratory status are not candidates for aggressive mobilization. For patients who cannot be actively mobilized, the task force recommended passive stretching, range of motion exercises, and/or neuromuscular electrical stimulation.

Table 4 summarizes the current evidence for use of early mobilization in the ICU.

Implementation

Implementation of early mobilization, as with other quality improvement projects, requires a structured approach and, often, a significant change in ICU culture. Translating evidence into practice requires summarizing the evidence for the intervention (set forth in the section on early mobilization, above), identifying organizational and cultural barriers to implementation, ensuring all appropriate patients receive the intervention, and measuring performance.[50]

Organizational and Cultural Barriers

Several organizational and cultural barriers specific to early mobilization must be acknowledged and managed. First, evidence suggests that the perceived barriers to mobilization and the level of activity achieved differs between nurses and physical therapists.[34] Thus, a multidisciplinary mobilization team that draws on the expertise of various healthcare providers may improve protocol compliance and patient outcomes. Furthermore, a national survey of acute care physical therapists revealed that 89% of hospitals require a physician consultation for initiation of physical therapy in the ICU, with established criteria for initiation of physical therapy in ICU patients present in only 10% of hospitals, and physical therapists automatically evaluating critically ill patients at only 1% of hospitals.[51] Creation and implementation of guidelines for automatic physical therapist assessment and initiation of activity therapy would likely benefit an early mobilization program. Combining daily sedation holidays with physical therapy sessions is a feasible and effective option.[11] Indeed, Thomsen *et al.* assessed patients before and after transfer to a RICU where early activity is a priority and found that the number of patients ambulating after 48 h in the RICU was 3-fold compared with pretransfer rates (P = 0.019). Although the APACHE II scores of the patient cohort did improve during the study period, the improvement was not enough to explain the significant improvement in activity. Thus, the authors concluded that the patients had been subject to "unnecessary immobilization" in ICUs where early mobilization is not embedded in the culture.

In addition, successful implementation requires addressing the issue of perceived cost and personnel needs. Although funding the intervention may be viewed as a barrier, implementation of a mobility team has not been associated with increased direct inpatient costs.[10] In fact, given the decreased ICU and hospital LOS associated with early mobilization, this intervention may prove to be cost-saving.[45]

Table 4. Evidence for Early Mobilization in the ICU: Outcomes

Study	Design	Patient Population	Intervention	Primary Endpoint	Major Findings
Burtin et al.[48]	Randomized controlled trial	90 medical/surgical ICU patients at a single center with an ICU LOS of at least 5 days and expected stay of at least another 7 days	20 min per day of passive or active bedside ergometry in addition to respiratory physiotherapy and standardized passive or active motion of the limbs vs. physiotherapy and standardized passive or active motion of the limbs alone	6-min walk distance at hospital discharge	Bedside ergometry was associated with a longer 6 min walk distance (29 *vs.* 25% predicted, $P < 0.05$) and a trend toward increased discharge to home (17% *vs.* 10%). There was no difference in weaning time, ICU LOS, or hospital LOS.
Schweickert *et al.*[11]	Randomized controlled trial	104 sedated patients in the medical ICU at two centers who had been on mechanical ventilation for less than 72 h and were expected to continue for at least another 24 h	Early exercise and mobilization (starting with active assisted range of motion exercises and progressing to bed mobility exercises, activities of daily living, transferring, and ambulating) during periods of daily sedation interruption *vs.* daily sedation interruption with therapy as ordered by the primary team	Number of patients returning to independent functional status at hospital discharge	Early exercise and mobilization was associated with increased return to independent functional status at hospital discharge, (59% vs. 35%, $P = 0.02$), less delirium (2.0 *vs.* 4.0 days with delirium, $P = 0.03$), more ventilator-free days (3.4 *vs.* 6.1, $P = 0.02$), and a trend toward increased discharge to home (43% *vs.* 24%, $P = 0.06$). ICU LOS, hospital LOS, and hospital mortality were similar in the two groups.
Morris *et al.*[10]	Prospective cohort study	330 medical ICU patients at a single center with acute respiratory failure requiring mechanical ventilation for less than 48 h	Mobilization by mobility team (nurse, nursing assistant, physical therapist) per mobility protocol (starting with passive range of motion and progressing to active resistance PT, sitting, and transferring) *vs.* usual care	Proportion of patients receiving physical therapy in patients surviving to hospital discharge	The mobility protocol was associated with more patients receiving at least one PT session (80% *vs.* 47%, $P \leq 0.001$), getting out of bed earlier (5 *vs.* 11 days, $P \leq 0.001$), and shorter ICU and hospital LOS (5.5 *vs.* 6.9 days, $P = 0.025$ and 11.2 *vs.* 14.5 days, $P = 0.006$, respectively)
Needham *et al.*[45]	Prospective before/after study	57 medical ICU patients at a single center mechanically ventilated for 4 days or more	Multifaceted intervention including creation of a multidisciplinary team; hiring of one full-time physical therapist, one full-time occupational therapist, and one part-time rehabilitation assistant; establishing guidelines for eligibility for early mobilization and PT/OT consultation; encouraging administration of sedating medications on an as needed basis in lieu of continuous infusions; changing the standard ICU admission orders default activity level from "bed rest" to "as tolerated"; and increasing consultations to psychiatry and neurology	Rehabilitation treatments, functional mobility, and sedation and delirium status	The median number of rehabilitation treatments per patient increased (1 *vs.* 7, $P < 0.002$), the proportion of treatments involving sitting or greater mobility increased (56% *vs.* 78%, $P = 0.03$), sedation requirements decreased (proportion of ICU days that patients received benzodiazepines, 50% *vs.* 25%, $P = 0.002$), and incidence of delirium decreased (days not delirious 21% *vs.* 53%, $P = 0.003$). ICU and hospital LOS decreased (by 2.1 days 95% CI: 0.4–3.8) and 3.1 days 95% CI: 0.3–5.9, respectively).
Martin *et al.*[44]	Retrospective analysis	49 previously bedridden chronic ventilator-dependent patients referred to a single tertiary care hospital ventilator rehabilitation unit	Whole body rehabilitation program (starting with improving trunk control and posture, progressing to resistance exercises, ergometry, ambulation, and staircase exercises)	Ventilatory weaning, muscle strength, and functional status	The rehabilitation program was associated with improved motor strength in the upper and lower limbs (1.9 at admission *vs.* 3.6 at discharge for upper limbs, $P < 0.001$, 1.5 *vs.* 2.7 for lower limbs, $P < 0.001$), increased functional independence (1.0 *vs.* 3.0 on 7-point functional independence measurement scale, $P < 0.001$). Upper extremity strength on admission inversely correlated with time to wean from the ventilator ($R^2 = 0.54$, $P < 0.001$).

ICU = intensive care unit; LOS = length of stay; OT = occupational therapy; PT = physical therapy.

Appropriate Patient Selection

Although the evidence suggests that early mobilization is safe and feasible in most ICU patients and may improve outcomes, the literature focuses primarily on medical ICU patients. Data on surgical and trauma ICU patients is lacking. Case reports of mobilization, such as those published in the left ventricular assist device and ECMO populations, provide only anecdotal evidence of the safety of this intervention in such patients. In addition, all of the studies on the safety, feasibility, and outcomes of early mobilization in the critically ill had exclusion criteria, many of them extensive. Early mobilization may not be appropriate in patients with severe derangements or acute deteriorations in circulatory or respiratory status, neurologic injury, ongoing myocardial ischemia, or severe agitation or delirium. Appropriate patient selection is required.

Measuring Performance

Using a metric for mobilization of ICU patients has several benefits. First, it allows providers to track patient progress throughout the ICU stay. As such, it could be utilized on rounds as an additional vital sign, providing practitioners with additional information on the patient's clinical status at that time, and reminding providers to consider early mobilization in every ICU patient. Second, the metric can be used in clinical research on early mobilization. And, finally, it may help in prognostication. However, no standardized metric for assessing mobility exists at this time. Kasotakis *et al.* developed the Surgical ICU Optimal Mobility Score, which consists of a "simple numeric scale that describes mobilization capacity of patients."[52] The score ranges from 0 to 4, with 0 corresponding to no activity and 4 corresponding to ambulation. The authors found that the Surgical ICU Optimal Mobility Score predicted mortality as well as ICU and hospital LOS, suggesting it can be used as a metric of severity of illness. Our center is in the process of defining and implementing a mobility score based on the maximal mobility performed by the patient each day.

Technological Advances and Future Directions

Technological advances may help facilitate delivery of early mobilization therapy in the ICU. A variety of technologies have been suggested for this purpose. First, portable medical equipment including cardiac monitors, pulse oximeters, infusions pumps, and mechanical ventilators are needed to allow patients to ambulate out of their ICU room. To facilitate patient ambulation, the Department of Biomedical Engineering at The Johns Hopkins Hospital created the MOVER aid.[53] The aid, whose name stands for "Moving Our patients for Very Early Rehabilitation," includes a walker with a built-in emergency seat should the patient need to sit down during therapy and an equipment tower that holds monitoring equipment, intravenous fluids, medications, infusion pumps, a portable ventilator, and two oxygen cylinders. Use of this pump decreases the number of personnel required to administer ambulation therapy to a patient.

Bedside cycle ergometry allows for passive, active-assisted, or active exercise, and has been shown to be safe, feasible, and effective in the critically ill.[48] Neuromuscular electrical stimulation (NMES) elicits muscle contraction *via* low-voltage electrical impulses delivered by skin electrodes.[53] NMES reduces disuse atrophy in healthy adults and chronically ill patients. Studies of NMES in the critically ill have shown mixed results, with some studies showing improved muscle strength[54,55] and decreased incidence of ICUAW,[56] and others showing no benefit.[57,58] Additional studies on NMES are ongoing.[59] The European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients recommends NMES "in patients who are unable to move spontaneously and at high risk of musculoskeletal dysfunction," although it is a level C recommendation.[49]

Recently, attention has turned to the use of video games, such as the Nintendo Wii (Nintendo, Kyoto, Japan), for mobilization and rehabilitation in the ICU. Video games can be played while sitting or standing, making them versatile for use in the ICU population. Massie *et al.* recently reported the use of "Wiihab" in six ICU patients.[60] Participation required use of major muscle groups, performance of fine movements, and mental effort. All patients showed evidence of increased physical effort (increased respiratory rate and heart rate). No adverse events were reported. Kho *et al.* published a case series of rehabilitation using the Wii in 22 medical ICU patients.[61] In this series, a total of 42 video game sessions took place, of which 69% occurred while standing and 45% while mechanically ventilated. The authors point out the potential advantages of video game therapy, including its short duration, low cost, and potential to help maintain patient interest and motivation. In their series, Kho *et al.* reported no safety events, although their CI was large. The risk of injury from Wii play is not negligible; case reports of recreational Wii play have described various fractures,[62,63] tendinitis,[64] and even a traumatic hemothorax.[65] Thus, further research is needed to delineate the safety of video game therapy in the ICU.

Other new technologies to increase implementation of early mobilization will likely arise, as electronic medical records and computerized order entry become more commonplace. Integration of mobility orders into the standard computerized ICU admission order set has already proven effective in increasing ICU patient activity.[66]

Nontechnological strategies to decrease ICUAW and improve early mobilization in the ICU are also being investigated. For instance, family participation in care of the critically ill may improve the family experience and benefit the patient.[67] A survey of ICU staff and family perceptions of family participation in care found that 100% of ICU physicians and 90% of nurses supported the idea, and 97% of families were willing to participate.[68] Seventy-seven percent of families viewed participation in helping staff change the patient's position in bed or transfer to a chair positively. However, only 13.8% of families participated in a care activity spontaneously. With appropriate training and supervision, families may be able to participate in early mobilization – assisting with position changes, transfers, and range of motion exercises – and significantly increase the amount of therapy provided each day.

Finally, development of drugs to target muscle-signaling pathways that mediate atrophy and hypertrophy is underway.[14] Initially, growth hormone was thought to be promising in this regard, but it was shown in a large randomized clinical trial to increase mortality in the critically ill.[69] Testosterone is another possibility, although there are concerns about related thrombogenesis and carcinogenesis. Novel approaches include inhibition of the muscle-specific ubiquitin ligases MURF-1 and atrogin-1 that normally promote atrophy, and activation of the hypertrophy pathway *via* IGF-1 and phosphoinositide 3-kinase.[14,70] Further evaluation of these targets is needed.

Conclusion

As survival from critical illness improves, there is increased appreciation for the sequelae of prolonged intensive care. Bedrest during critical illness can no longer be considered a benign intervention, as it is associated with catabolism, atrophy, and ICU-acquired weakness. Neuromuscular weakness is commonplace in the ICU and can persist for years after discharge. Early mobilization is a safe and feasible intervention for many critically ill patients, and is associated with improved outcomes. Initiation of an early mobilization program requires culture change and technology may be helpful in increasing compliance. Further research on early mobilization in the ICU and potential drug targets is warranted.

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