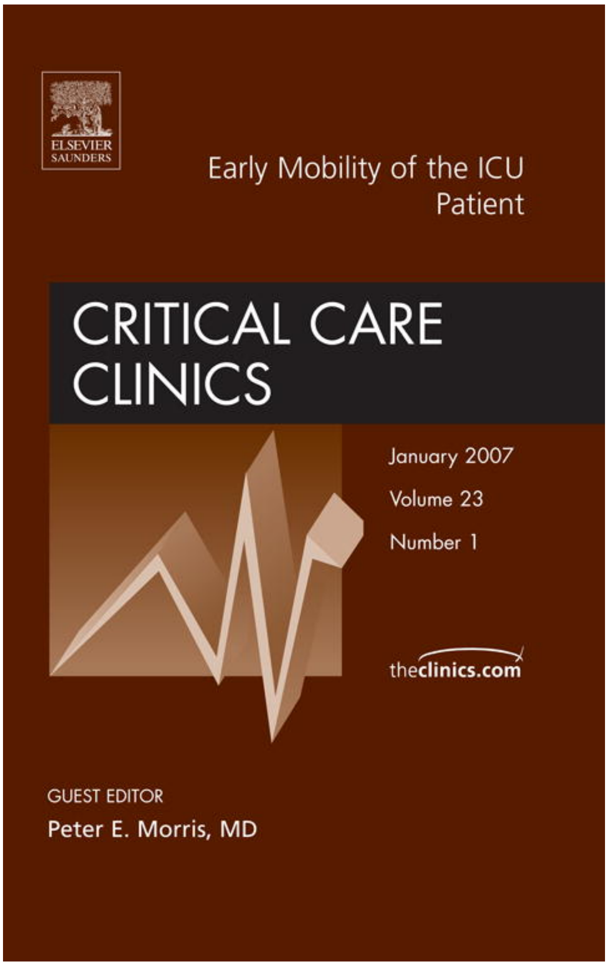
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Early Intensive Care Unit Mobility: Future Directions

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Muscle, nerve and brain dysfunction represent the major long-term morbidities after an episode of critical illness [1–3]. The organ systems that have the greatest impact on functional and quality of life outcomes after severe critical illness are very difficult to assess and monitor during the intensive care unit (ICU) stay, and thus are effectively ignored during the acute course of critical illness. This issue of *Critical Care Clinics* challenges us to consider how we might change the natural history of nerve and muscle organ dysfunction through early intervention during the ICU stay. This is a significant challenge indeed, because at this point we know so very little about the pathophysiology of these lesions, which aspects are remediable, and the nature and timing of an appropriate intervention.

In the previous articles of this issue, care of the critically ill patient was explored from the viewpoint of how ICU mobilization may benefit patients, and how our usual practice may impede the delivery of early mobilization. In this article, the authors discuss the future directions in this area under the following headings: current limitations in understanding the effect of immobility on muscle and nerve, uncertainty about the risks and benefits of early mobility, how to implement early mobility programs, and ICU process of care issues required to facilitate early mobilization. Finally, we present a ‘‘roadmap’’ that outlines future directions as we move toward the development and testing of early ICU mobility therapies.

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Effect of immobility on nerve and muscle

Current practice

One significant obstacle in our understanding and development of early mobility programs is a poor knowledge of current practice. To date, there are very few published survey data that describe either current physiotherapy resources or early mobility practice patterns across different regions of the world. Norrenberg and Vincent [4] published the results of a questionnaire to which over 100 directors of physiotherapy in European hospitals responded. Forty-eight percent of responders were from University hospitals, and over 45% had greater than 700 beds. Fifty percent had over 24 ICU beds, and 38% of the facilities had more than 30 physiotherapists on staff. In 100% of the units, in contrast to physical therapists in the US, the physiotherapists also performed some respiratory therapy in the setting of mobilization and positioning. This serves to highlight how varied physiotherapy resources may be, and that many staff members may be required to assume a multiplicity of duties that may be unrelated to early range of motion and mobilization.

Questionnaires such are these are very useful to describe current practice. It would be very helpful to know if there are any organized efforts to institute early mobility, what they are, how effectively they have been implemented, and whether they were felt to be an important early intervention during the ICU stay. Furthermore, there are no data to help us understand whether clinicians are aware of current long-term outcome data on acute respiratory failure patients. Such surveys could determine whether there is a perceived need for an ICU-based, early intervention program to modify longer-term dysfunction. Early priorities, therefore, should be to characterize current practice pattern variability in detail, and to describe current attitudes toward outcome data. These data are crucial to inform the development of ICU-based early mobility programs.

Barriers to implementation

There are many potential reasons why it might be difficult to implement an early mobility program in critically ill patients. These were outlined by Morris elsewhere in this issue, and include safety issues, multiplicity of vascular access, cost, obesity, and time constraints. This discussion was extrapolated from a literature on chronic disease states for which there are established rehabilitation programs, because these data do not exist for populations of critically ill patients. Clearly, the dominant concern is that of safety, and in the absence of data that unequivocally support the benefit of early mobility, it is very challenging to push this agenda forward. This again underscores the need for descriptive survey data to elucidate the perceptions of the members of the multidisciplinary team, and to highlight important concerns and educational needs as we move toward formalized testing of early ICU-based rehabilitation programs.

Paucity of data on muscle and nerve injury and recovery

In addition to a dearth of information on current practice and potential barriers to the wide adoption of early ICU mobility, there is also a real deficit in our understanding of the nature of muscle and nerve injury and recovery.

Muscle injury

Deconditioning in the ICU patient, or what practitioners may refer to as primary muscle atrophy, may represent an important contributor to muscle weakness. The isolated effect of primary muscle atrophy in the critically ill patient has not been extensively studied and remains poorly characterized. Secondary atrophy may be defined as the presence of primary atrophy with a secondary pathological insult-like inflammation. The phenomenon of secondary atrophy may be most relevant to the weakness of critical illness, and represents a significant challenge in trying to understand the nature and mechanism of discrete contributors to muscle injury because of its multifactorial nature. We understand that antigravity muscles (eg, in the calf and back) may lose strength rapidly with bed rest, and that there is accelerated proteolysis in muscle in inflammatory disease states (eg, sepsis). The muscle inflammatory component may result in the activation of the ubiquitin-dependent proteolytic and calpain systems. For ICU patients, there is an additional concern that muscle may undergo ‘‘functional denervation’’ related to a decrease in frequency and intensity of nerve impulses arriving at the muscle membrane. This may have implications for muscle mitochondrial content and oxidative capacity. Thus, at low workloads, critically ill patients may be more dependent than in the pre-illness state, on glycolysis with lactate formation. Early in their recovery, critically ill patients may have significant fatigability even with modest movement (ie, assuming an upright position, standing at the bedside). A recent study by Di Giovanni and colleagues [5] showed that only patients who have critical illness myopathy (CIM) had evidence of activation of the transforming growth factor (TGF)-beta/mitogen-activated protein kinase (MAPK) pathway, whereas activation of the ubiquitine ligase pathway was common to both neurogenic and myogenic atrophy.

Nerve injury

The pathogenesis of critical illness polyneuropathy (CIP) has been linked to a perturbation in the microcirculation, leading to nerve injury. There has been a recent report of increased expression of E-selectin on the endoneurial and epineurial vessels of peripheral nerves in septic patients, and this has been shown to be mediated by proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 [6]. There is also a disruption of nerve action potential that may be functional and not structural early on in the course of the disease [7].

There are many and varied challenges that lie ahead in our understanding of CIP and CIM, despite the significant advances that have been made to date. DeJonghe and colleagues [8] have prospectively estimated the incidence of CIP to be as high as 25% in ICU patients who achieved awakening and with more than 7 days of mechanical ventilation. Despite this work, the true incidence of CIM and CIP is likely underestimated worldwide. There are no studies that have prospectively evaluated the development and resolution of these failed organ systems from ICU admission to some follow-up time point when the patient has regained functional status. The proportion of patients who have these conditions will vary widely depending on case mix, and some authors have argued that the denominator for the calculation of proportion affected should be those who have at least one failed organ system using the sequential organ failure assessment (SOFA) score [9]. Clearly, this is an important complicating factor in trying to understand how common these problems are. Future studies may need to combine serial muscle biopsies with detailed physiological and bedside testing. All patients who have weakness will not necessarily have structural muscle or nerve changes, so this adds another degree of complexity in trying to understand the spectrum of functional to structural muscle and nerve disorders. In addition, tissue samples for molecular and genetic studies will be necessary to help further understand the pathophysiology. These precious samples will help gain a better understanding of the critically ill population that is at risk for development of these conditions. The efficient identification of the at-risk population may be the primary issue. Better knowledge of susceptible populations will allow bedside practitioners to specifically target these groups for an early intervention program.

Intensive care unit and non-intensive care unit models for future mobility program structure

Uncertainty about risks and benefits of an early mobility program

This article has already discussed the limitations in our understanding of current practice, and our current inability to identify those critically ill patients who are at risk for muscle and nerve organ dysfunction. The exact nature of risks and benefits associated with an early ICU mobility program are also unclear. It would be particularly important for critical care practitioners to know what, if any, are the absolute contraindications to the initiation of mobilization therapy in ICU patients (Box 1).

This next section discusses some of the lessons learned from other disease states and their specific rehabilitation and exercise programs. Information

Box 1. Safety parameters to be addressed in future mobility studies

- Ventilator settings at which mobilization should be withheld?
- Fever is known to increase oxygen consumption—should mobilization be held in febrile patients?
- Is there a dose of norepinepherine that predicts harm if mobilization occurs?
- How soon after respiratory failure or shock should mobilization be implemented?
- How do we select the appropriate mode and intensity of mobilization?
- What is appropriate action if a decrease in oxygenation or blood pressure occurs? Stop mobility therapy versus increase in supportive therapies for oxygenation (fractional inspired oxygen concentration [FiO2], positive end-expiratory pressure [PEEP]) and shock (fluid, pressors, blood)?

from these programs may serve as a valuable starting point from which specific programs for survivors of critical illness may be adapted.

Modeling on pulmonary rehabilitation programs

There are many valuable principles that may be adapted from pulmonary rehabilitation programs and applied to the development of early ICU mobility interventions. One might begin by suggesting that the current tenets of the pulmonary rehabilitation program should be adopted by any program of early intervention in ICU. These include the alleviation of symptoms, restoration of maximal functional capacity, and reduction in handicap to optimize quality of life outcomes [10]. The pulmonary rehabilitation program serves as an instructive model for the development of a multidisciplinary team that employs multiple modalities of exercise training, psychosocial support, and education through the illness trajectory, from the acute hospitalization to community reintegration. Finally, this model has been evaluated through randomized controlled trials to understand whether it truly represents an advance in patient care. Any early ICU intervention will also need to meet these same rigorous testing standards before its wide adoption as part of current clinical practice (Box 2).

Pulmonary rehabilitation programs have been successful in understanding how to stratify patient populations to better understand who will benefit most from this intervention. It is crucial to understand how to characterize the at-risk population, so that different interventions with varying intensity may be applied appropriately, and expectations for significant outcome improvement are robust and realistic. It is also imperative to determine relative

Box 2. Future questions for ICU mobility therapy

- Who is responsible for passive range of motion?
- When to start ICU physical activity?
- What is safe change in heart rate (HR), O2 saturation?
- What is baseline HR?
- How do we measure exercise load for ICU patients?
- How do we judge appropriate dose of therapy and optimize the benefits of therapy?

and absolute contraindications that may preclude any clinical benefit and only impart harm.

The structure of the multidisciplinary team and inclusion of physiatry, physical, occupational, and respiratory therapists, and nurses, nutritionists, psychologists, and social workers may serve as an excellent template for the construction of the early ICU mobility team. It may also be helpful to evaluate the different components of the training program itself, including the type, frequency, intensity, and specificity of exercise training, in addition to the type of educational programs used and psychosocial or behavioral interventions.

These same principles of population stratification, an understanding of absolute contraindications for an intervention, realistic expectations for outcome, and the development of a team approach based on pre-existing multidisciplinary models will be informative as we develop, pilot, and then formally test early mobility programs.

Stroke rehabilitation

Additional insights may be gleaned from the stroke rehabilitation literature as well. These include the development and use of clinical tools to standardize disability, an understanding of how to stratify patient populations in order to address specific needs, and how to apply an optimal intervention within an optimal time frame and to understand the predictors of returning to home or functional independence. The stroke literature uses the functional independence measure (FIM) scores to stratify their patients [11]. These scores enable physicians to stratify populations according to post-stroke functional status, so that programs can be appropriately tailored to meet needs. It also provides a valuable metric to monitor patient improvement and formally evaluate the impact of an intervention.

Studies based on patient stratification using the FIM scoring system have helped physicians treating stroke patients to realize better outcome by identifying rehabilitation needs related to degree of functional impairment. Teasall and colleagues [12] were able to show that patients who had severe stroke and who received individualized care on a highly specialized stroke rehabilitation unit achieved impressive outcomes. They found that many patients were no longer wheelchair bound, and almost half returned home. They concluded that this group of patients who historically were felt to have very poor outcomes should not be excluded from active rehabilitation programs.

It is also important to understand as many of the potential determinants and modifiers of outcome as possible. One important determinant of functional outcomes in stroke patients is the timing of the intervention. In a recent study, Salter and others [13] showed that patients admitted to stroke rehabilitation within 30 days of a first-ever unilateral stroke had greater functional gains and a shorter length of stay that those whose rehabilitation admission was delayed beyond 30 days.

How to implement early intensive care unit mobility programs—examples of programs targeting early intensive care unit mobility

Early mobilization of left ventricular assist device recipients

Left ventricular assist device (LVAD) recipients are typically severely deconditioned, and may require prolonged periods of mechanical ventilatory support. The time spent in ICU may be associated with prolonged periods of bed rest, and this may lead to a devastating loss of muscle mass and functional ability. Perme and colleagues [14] reported on one of their LVAD patients who had significant improvement in functional status after the introduction of their own early mobilization program, and they provide a valuable discussion of their physical therapy evaluation, intervention, and safety criteria.

This program incorporates many of the important principles outlined in the discussion of the pulmonary and stroke rehabilitation programs. There is comprehensive screening early after ICU admission to maximize the recognition of eligible patients. Patients are stratified based on severity of illness and safety, and they are supported with high-flow oxygen and portable ventilators to promote early ambulation. A multidisciplinary model was employed, and there was close communication among members of the team to optimize safety, timing, and duration of the early mobilization intervention.

Specialized unit approach to early intensive care unit mobility

Researchers at the LDS Hospital in Salt Lake City, Utah have reported their experience in delivering early ICU mobility therapy [15]. They evaluated an early mobility pilot program within their respiratory intensive care unit, and this protocolized delivery of physical therapy was administered regularly to mechanically ventilated, acute respiratory failure patients. Patients underwent daily eligibility screening for early mobility therapy.

There were no reported adverse events as a result of early mobility. A majority of survivors (69%) were able to walk more than 100 feet by the time of discharge from ICU, and this report concluded that early activity is feasible and safe in acute respiratory failure patients.

Experience with an early intensive care unit mobility team

An alternative approach to the delivery of early ICU mobility therapy was recently reported from Wake Forest University in Winston-Salem, North Carolina [16]. Administering early ICU mobility therapy to acute respiratory failure patients was accomplished via an ICU mobility team composed of nursing assistants, nurses, and physical therapists who communicated closely with other members of the ICU team. Initiation of protocolized mobility therapy started on the first day of ICU admission and consisted, initially, of passive range of motion three times per day in the non-awake ICU patient. When sufficiently alert, the patient participated in a daily graded physical therapy program until discharged from the ICU.

Process of care issues required for early mobilization

Daily disruption of sedation

One element that may promote adherence to daily awakening programs is the additional daily assessment of patients' ability to partake in ICU active mobility programs. Together with formal protocols to withhold sedation when appropriate, daily protocols to establish when an ICU patient is able to understand instruction and perform simple commands for a physical therapist may serve a dual purpose and provide benefit.

Promoting the culture of a more awake patient

There are significant challenges and potential risks to patients when agitation is present. An ICU environment that fosters wakefulness may be achieved more consistently through the development of mobility safety data. These data would necessarily be the result of careful pilot testing during the development of a more formal early mobility intervention, and may help define specific ICU clinical parameters that are predictive of harm if wakefulness or mobility is attempted. Additionally, ongoing interaction with ICU mobility programs may give support to the safety of wakefulness in the ICU environment.

Early tracheostomy to facilitate mobilization

Elsewhere in this issue, Drs Clum and Rumbak explore the risks and benefits of tracheostomy in mechanically ventilated patients. The data from their prospective trial of medical ICU patients described a potential outcome benefit in morbidity and mortality when early (within 48 hours of admission) versus late tracheostomy was performed [17]. This study reinforces the retrospective findings of other investigators who reported an advantage in early tracheostomy for acute respiratory failure patients [18–20]. These retrospective reports were clearly limited by confounding indication, but were hypothesis-generating in terms of the potential benefit of early tracheostomy. Different purported mechanisms have included a reduction in dead space, decrease in amount of sedation given, and less concern about patient safety for early mobilization. All of these hypotheses await further investigation.

Rehabilitation programs and the exclusion of the medically critically ill—seventy-five percent rule for US rehabilitation hospitals

The 75% rule underscores how survivors of critical illness are potentially discriminated against in terms of their access to inpatient rehabilitation in the United States. This rule outlines the conditions for reimbursement from the Centers for Medicare and Medicaid (CMS) to rehabilitation hospitals in the United States. It stipulates that during a 1-year period, at least 75% of the patients in a rehabilitation hospital have one of 13 identified conditions (Box 3). In the United States, the 75% rule is being phased in, with full compliance required by July 1, 2007, and specifically excludes patients whose illness started with primary cardiac or pulmonary disorders.

Box 3. Thirteen approved diagnoses for admission to inpatient rehabilitation facilities

- Active, polyarthricular arthritis
- Amputation
- Brain injury
- Burns
- Congenital deformity
- Fracture of the femur (hip fracture)
- Trauma
- Neurological disorders, including multiple sclerosis, motor neuron diseases, polyneuropathy, muscular dystrophy, and Parkinson's disease
- Osteoarthritis
- Spinal cord injury
- Stroke
- Systemic vasculidities
- Knee or hip joint replacement

The 75% rule was created in 1983, and has been reviewed by experts at the Institute of Medicine and supported with Congressional testimony from representatives of CMS as recently as 2005 [21]. It was initially adopted to identify those hospitals that would be eligible for exemption from the inpatient prospective payment system (IPPS) and would continue to be reimbursed based on costs [21]. Since the institution of the inpatient rehabilitation facilities (IRF) IPPS, CMS no longer reimburses IRFs on a cost basis; however, the IRF IPPS provides higher payment levels than would be paid for these cases under the IPPS.

The alternatives to IRFs for medical ICU patients who have significant rehabilitative needs include treatment in an acute care hospital, skilled nursing facility, long-term acute care hospital (LTAC), or simply waiting until the patient is medically stable for outpatient rehabilitation and home health care.

There is an important body of outcomes literature, and this should be used to educate current funding agencies about the rehabilitative needs of survivors of critical illness. In addition, critical care experts have a responsibility to work closely with colleagues in rehabilitation medicine to evaluate and quantify specific needs in ICU survivors, in order to construct appropriate clinical pathways for these patients and to inform insurance carriers, the Institute of Medicine and CMS of the significant unmet needs of these patients.

Roadmap for future intensive care unit mobility therapy

How should we monitor and diagnose muscle and nerve dysfunction in intensive care units?

We still have very little detailed understanding of the characteristics, determinants, modifiers, and natural history of nerve and muscle damage acquired during the ICU stay. We understand that patients have demonstrable weakness within 7 days of their ICU stay [8], and that this can be assessed using the MRC scoring system in the more awake patient at the bedside in ICU. In the deeply sedated, unresponsive patient, it is very difficult to conduct any meaningful or reliable longitudinal evaluation of nerve or muscle function. We have some limited data from electromyography, nerve conduction study, and muscle biopsies that give us some insights, but the spectrum of injury and its evolution during the ICU stay is completely unknown at this time. And, although early ICU mobility seems inherently to be a good and beneficial intervention, there is no high-level evidence that early or intensive physical rehabilitation improves this muscle and nerve injury beyond what would have been normal recovery for that individual patient.

Intensive care unit follow-up clinics

Post-ICU follow-up clinics have been in existence in the United Kingdom for almost 20 years, and this effort has largely been pioneered by Griffiths and Jones [1]. They have elevated awareness of the importance of long-term follow-up for patients and their caregivers, members of the ICU multidisciplinary team, and society. As a result of these efforts, the vital importance of post-ICU patient follow-up was acknowledged by the Audit Commission of UK critical care services in 1999 [22] and the UK government white paper, *Comprehensive Critical Care*, in 2000 [23]. Efforts to evaluate long-term outcomes after critical illness in North America have been more recent, and have focused on survivors of lung injury, acute respiratory distress syndrome (ARDS), and older patient populations [2,3,24–28]. Follow-up programs and clinics represent a unique opportunity to enumerate the multiple physical and neuropsychological consequences of critical illness [29]. They may also be viewed as a potentially valuable resource when trying to evaluate the long-term impact of ICU-based interventions. For there to be wide adoption of ICU early mobility programs, we must be able to rigorously study and test this intervention, and to determine if it results in improved physical outcome measures. The ICU follow-up clinic structure may facilitate this evaluation. In addition, if early intervention proves to be beneficial, it may be incorporated into a longer-term physical rehabilitation program, so that there is a seamless transition from ICU through inpatient and outpatient rehabilitation care.

Professional roles in the delivery of early intensive care unit mobility: who should be responsible?

The practice and pattern of early mobility in ICU remain unclear. As mentioned earlier in this article, there has not been any concerted effort to date to systematically audit and review current practice across multiple centers or countries. For example, it is not at all clear who delivers passive and active range of motion during the ICU stay, and this task might not only be undertaken by allied health professionals, but in some instances by family members or loved ones. Current review of practice is a vital starting point to understand how responsibility for early mobility is prescribed, and how it relates to local opinion on the utility of early mobility, resource availability, and local expertise. It will be important for future studies to have a better understanding of practice pattern variability, because these tasks will not obviously fall directly to a specific professional group. Delivery of ICU mobility may be variable across allied health professionals, but also across ICUs within the same hospital.

Following the ascertainment of current practice pattern variability, the prototype for the early ICU mobility intervention will need to be constructed by review of relevant literature, expert opinion, and further refinement through single-center pilot testing. This intervention will then require formal evaluation as part of a cluster-randomized interventional study to determine if it improves outcomes of physical functioning, quality of life, and the incremental cost associated with these outcome improvements.

Intensive care unit outcome clinics may facilitate measurement of these various outcomes. Having a more comprehensive understanding of the attendant risk associated with early mobility programs will help diminish the reservations of some practitioners that movement could hurt a critically ill patient by inducing a dysrhythmia, an episode of hypoxemia, or pulmonary embolism. The opportunity to explore risk will be essential for informed consent and safety concerns during the conduct of a larger trial. In addition, detailed evaluation of potential harm during the pilot studies will aid in the construction of recommendations for complex clinical situations that would complicate this therapy in ICU patients—the multiplicity of vascular access devices, coagulopathy risks (high international normalized ratio [INR], low platelets, uremia, or other platelet dysfunction syndromes) (see Box 1). In addition, early pilot studies would help to elucidate the issue of optimal timing for initiation of either passive or active range of motion therapy, and how quickly physical therapy should be accelerated during the ICU stay.

In addition, it will be a significant challenge to understand how to implement early mobility in the context of so many competing tasks and therapies. There are competing time needs for the delivery of ICU care within the Monday through Friday, 8 AM to 5 PM time frame. Patients are transported for surgery and other procedures, and there is the added complexity of coordinating this with daily awakenings, dialysis, phereses, wound care, spontaneous breathing trials, and trach mask trials. The addition of mobility care will need to be supported by data to prioritize its inclusion as part of daily care.

Summary

The concept of early mobilization during an episode of critical illness is appealing, and one that intuitively appears to make sense and offer benefit, but its utility remains unclear. Currently there is much uncertainty about the nature of ICU-acquired muscle wasting and weakness, its determinants, modifiers, and natural history. Not only do we know so little about the nature of the physical lesion, we also know virtually nothing about current attitudes and practice in early ICU mobility. In addition, we do not have a sense of the critical components of the intervention—time to administration, quantity, duration, intensity, frequency, and how to achieve standardization and acceptability—and how it should be derived before formal testing. This article has suggested that insights from established interventional programs in pulmonary rehabilitation and stroke rehabilitation may serve as valuable resources to inform the development of an early ICU mobility intervention. ICU follow-up clinics may prove to be an important vehicle to capture the early and late impact of this ICU-based intervention on longer-term physical function and quality of life outcomes. We will need to pilot-test our intervention, and ultimately subject it to a cluster randomized trial to determine efficacy.

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