

REVIEW

Mobilization in Severe Sepsis: An Integrative Review

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Severe sepsis is a leading cause of long-term morbidity in the United States. Up to half of severe sepsis is treated in non-intensive care unit (ICU) settings, making it applicable to hospitalist practice. Evidence has demonstrated benefits from physical therapy (PT) in myriad conditions; whether PT may benefit severe sepsis patients either within or outside the ICU is unknown. Therefore, we conducted a review of the literature to understand whether early mobilization improves outcomes in patients with severe sepsis in non-ICU settings. We summarized the pathophysiology of functional decline in severe sepsis, the efficacy of PT in other patient populations, and the potential rationale for PT interventions in patients with severe sepsis. Multiple databases were searched for keywords including length of stay, mortality, costs, mobilization, and PT. Two authors (S.G. and V.C.) independently determined the eligibility of each study.

A secondary review including studies of any infectious pathology with PT interventions or sepsis patients within the ICU was also conducted. Our search did not yield any primary literature regarding the impact of mobilization on severe sepsis outcomes in non-ICU settings. Only 1 retrospective study showed potential benefit of therapy in sepsis patients in the ICU. Similarly, in non-ICU settings, only 1 study that included patients with bacterial pneumonia reported outcomes after implementing an intervention consisting of early mobilization. These findings suggest that scant data regarding the efficacy of early mobilization following severe sepsis exist. Because hospitalists often care for this patient population, an opportunity for research in this area exists. *Journal of Hospital Medicine* 2015;10:54–59. © 2014 Society of Hospital Medicine

Severe sepsis, defined as an infection leading to systemic inflammatory response and acute organ dysfunction, is a significant cause of morbidity and mortality.^{1–3} Although it has been a condition classically attributed to patients in the intensive care unit (ICU), accumulating data suggest that a substantial proportion of patients with severe sepsis are managed by hospitalists and floor teams in non-ICU, general ward settings.^{1,4,5} Although the incidence of severe sepsis continues to rise both in the United States and other developed nations,^{2,6,7} advances in early recognition, management, and care of this condition have resulted in improved rates of survival.⁸ The resultant increase in a “severe sepsis survivor population”⁶ make the long-term sequelae of this condition an important public health problem.⁹

In both the ICU and on general wards, severe sepsis survivors suffer from decreased functional status, worsened quality of life, increased cognitive dysfunction, and sarcopenia.^{4,6,10–14} Not surprisingly, many such patients are discharged to long-term care facilities for physical rehabilitation,¹⁵ with escalating utili-

zation of resources¹⁶ and cost.^{17,18} Inexpensive interventions that improve outcomes following sepsis would thus be welcomed.

It is well known that physical therapy (PT) and early mobilization are beneficial in mitigating functional decline in a number of conditions.^{19–22} PT can improve outcomes in several ways: prevention of bed rest deconditioning, mitigation of mechanisms that lead to sarcopenia, increased pulmonary and tissue aerobic capacity, and improved sense of well-being. Indeed, among the population cared for in ICU settings, early mobility and PT lead to more ventilator-free days, better functional status at discharge, shorter duration of delirium, and even a potentially reduced risk of central line-associated bloodstream infection (CLABSI).^{23,24} However, whether initiating early PT can improve outcomes in patients with severe sepsis treated by either intensivists or hospitalists/floor teams outside the ICU is unknown.

Therefore, to better understand this phenomenon, we systematically reviewed and integrated the literature regarding early mobilization and PT for severe sepsis outside the ICU. To be more inclusive, a secondary review including populations with any infectious etiology and severe sepsis treated within the ICU was also conducted. Our review begins by providing an overview of the pathophysiology behind functional decline in severe sepsis, along with existing evidence on early mobilization efficacy in other patient populations. We then proceed with a review of the extant literature on the aforementioned topic. We conclude with an evaluation of the current evidence on the

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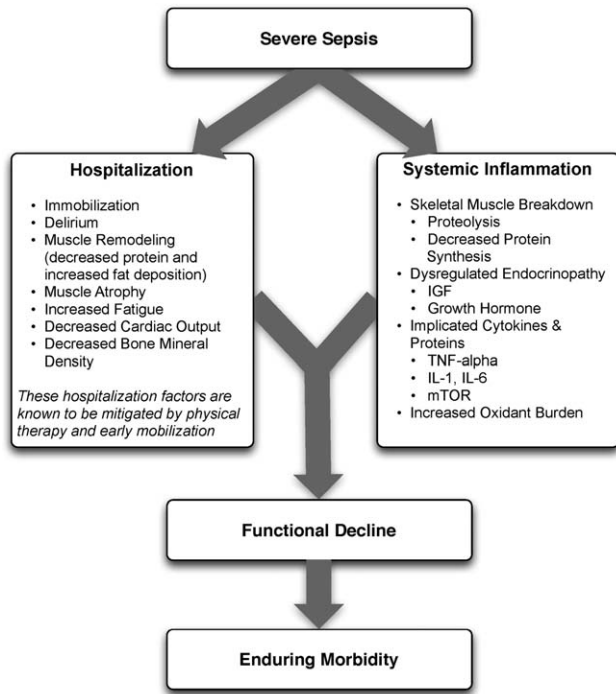


FIG. 1. Sepsis and functional decline diagram. Abbreviations: IGF, insulin-like growth factor; IL, interleukin; mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor.

subject, along with assertions regarding future research in the area.

PATHOPHYSIOLOGY OF DISABILITY FOLLOWING HOSPITALIZATION FOR SEVERE SEPSIS

The pathophysiology behind functional decline in patients hospitalized with severe sepsis is multifactorial (Figure 1). During hospitalization, it is well known that patients suffer from restricted mobility,²⁵ and that this impediment is linked to poor functional outcomes.²⁶ Described as far back as Hippocrates,²⁷ more recent studies have elucidated how prolonged bed rest leads to a multitude of physiological changes that promote deconditioning.²⁸ Specifically, skeletal muscle atrophy and decreased protein synthesis, independent of ongoing disease processes and acute illness, have been demonstrated in both animal and human models of prolonged inactivity.^{29,30} Additionally, bed rest leading to insensible fluid losses, a decline in stroke volume and effective cardiac output, bone loss, and decreased insulin sensitivity has been reported.^{28,31} There is little doubt that the aforementioned issues pertain to severe sepsis patients outside the ICU. In fact, nearly all of the acute mechanisms driving Creditor's "hazards of hospitalization" are noted among patients with severe sepsis.³²

Furthermore, several factors preceding hospitalization may increase risk of disability. For example, Covinsky et al. described a number of risk factors, such as comorbid conditions, cognitive impairment, and various psychosocial aspects such as depression

and limited social support, as being associated with increased risk of functional decline.³³ Thus, both in-hospital and prehospital factors likely combine within an individual patient's context to determine risk of physical decline.

On this backdrop and the inherent immobilization associated with hospitalization, sepsis and inflammation catalyze physiologic changes that further propagate deconditioning.⁷ Implicated pathways and proteins for this process include the mammalian target of rapamycin, human growth hormone, insulin-like growth factors, interleukin-1, and tumor necrosis factor- α . Through several metabolic alterations, sepsis independently promotes skeletal muscle breakdown and impairs skeletal muscle synthesis.^{34–36} Inflammation associated with sepsis also increases oxidant burden, further leading to muscle dysfunction and dysregulation.^{7,31,37,38}

EFFECTS OF PHYSICAL THERAPY AND MOBILIZATION ON CLINICAL OUTCOMES

In patients with nonsepsis conditions who are at risk for functional decline, the effectiveness of physical therapy has been studied in multiple settings with positive outcomes. For example, in hospitalized elderly patients with general deconditioning, PT-based interventions have demonstrated reductions in length of hospital stay.³⁹ Additionally, exercise in healthy subjects who have been subjected to bed rest has been shown to attenuate physiological changes, and maintain plasma and red cell volume and work capacity.⁴⁰ Adequate safety and improved outcomes have also been demonstrated in the general population of critically ill patients who receive early PT and mobilization. Improved functional capacity at discharge, decreases in duration of delirium, increased ventilator-free days, decreased risk for CLABSI, and a better general sense of well-being following these interventions have been widely reported in the literature.^{14,19,23,24,41–45} Interestingly, critically ill patients may have a dose- and time-dependent response to PT; that is, high intensity and early onset mobility-based interventions are often associated with more ventilator-free time and improved functional outcomes, resulting in shorter ICU and hospital length of stay.^{42,46–48}

Moderate intensity exercise has also been shown to improve 6-minute walking distance in patients convalescing from coronary artery bypass grafting surgery.⁴⁹ Furthermore, in the postoperative setting, patients suffering traumatic hip fractures are known to benefit from physical and occupational therapies with shorter time to ambulation and improved locomotion in the recovery period.^{21,50,51} Among patients with stroke, PT and gait training has led to improvements in speed, gait, independence during walking, activities of daily living, and extended activities of daily living.^{52–54} A recent meta-analysis also suggested that

extra PT compared to regular treatment in patients with acute and subacute conditions such as stroke and postoperative states improved mobility and quality of life, while reducing length of hospital stay.²²

Although this evidence suggests potential benefits for PT and mobilization, it is important to note that the effect of these treatments in dissimilar populations is unknown and may not necessarily be positive. For example, a recent study examining PT and its impact on patients with hip osteoarthritis showed no clinical benefit.⁵⁵ Mobilizing patients in severe illness may be associated with important risks, including falls, worsening of their clinical status, or moral discouragement in the setting of limited capacity. Therefore, understanding which elements of mobilization efforts create the greatest impact in the context of delivery of the intervention is critical to assessing the risk, benefit, and efficacy of PT-based interventions.

EARLY PHYSICAL THERAPY FOR SEVERE SEPSIS OUTSIDE THE ICU: LITERATURE REVIEW

Given the functional decline associated with severe sepsis and the evidence of PT efficacy in other populations, we reviewed the current literature for studies evaluating physical therapy in severe sepsis patients outside the ICU. With the assistance of medical reference librarians, we searched MEDLINE via PubMed (1950–present), EMBASE (1946–present), Cochrane CENTRAL Register of Controlled Trials, and the Cochrane Database of Reviews of Effectiveness (1960–present via Ovid). The search was last updated in June 2014.

We searched for studies that (1) involved human patients ≥ 18 years of age, (2) included patients with a primary diagnosis of sepsis or severe sepsis being treated outside the ICU, (3) featured a primary intervention that included PT or an early mobilization-based initiative, and (4) reported a primary clinical or functional outcome of interest. *Early* was defined based on the included studies' definition. To be fully inclusive, we also conducted a secondary review with inclusion criteria expanded to studies of either any infectious pathology or severe sepsis patient in the ICU that employed PT interventions.

Our electronic search retrieved 815 records (Figure 2). Despite this approach, no publications met our primary inclusion criteria as we found no study that implemented a mobility intervention directed toward patients with sepsis treated outside the ICU. Our expanded secondary review included patients with any infectious pathology or those with severe sepsis in the ICU treated with PT; in this review, 2 studies met eligibility criteria.⁵⁶ In a 2003 cluster-randomized trial, Mundy and colleagues randomized patients admitted with pneumonia to receive early PT or usual care. The outcomes of interest were hospital length of stay, mortality, number of chest radiographs, emergency

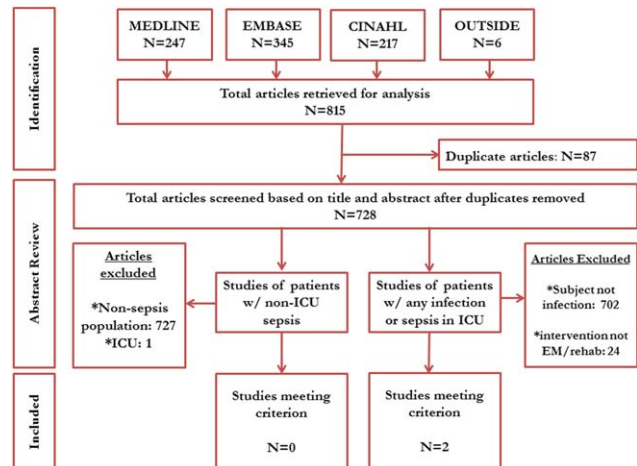


FIG. 2. Systematic review flowchart. Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; ICU, intensive care unit; EM, early mobilization.

department visits, and readmissions at 30 and 90 days after hospital admission. Although the study has important limitations (including patient-level difference between trial arms, subjective definition of early mobilization), the authors found a significant decrease in length of stay among patients with pneumonia who received early PT compared to controls (5.8 vs 6.9 days, absolute difference 1.1 days, 95% confidence interval: 0–2.2 days). The study also reported a substantial decrease in adjusted mean hospital charges for the early mobilization group versus the usual care group (\$10,159 per patient vs. \$12,868 per patient, $P = 0.05$). In the second study, Sossdorf et al. retrospectively evaluated a cohort of 999 patients with severe sepsis and septic shock and assessed whether onset and frequency of PT-based interventions was associated with clinical benefit. After multivariate analysis, the authors reported a small mortality benefit associated with the relative number of PT interventions (hazard ratio: 0.982, $P < 0.001$).⁴⁵

EXPLAINING THE VOID

Our integrative review of the current literature reveals a gap in our understanding of the role of early mobilization in severe sepsis both within and beyond the ICU. Given the promise of PT-based interventions and the toll of severe sepsis, one must ask: why may this be so?

First, the understanding that severe sepsis leads to significant, long-term consequences for survivors has only been identified recently. Thus, it is possible that the burden and consequences related to this condition have not been fully recognized in clinical settings, leading to a paucity of research and interventions. Although the association between sepsis and mortality has been known since the 1990s,⁵⁷ long-term complications and enduring morbidity of this disease continue to be realized. Indeed, many studies delineating the longer-term effects of sepsis have been only recently published.^{6,10–13}

Second, it is likely that many clinicians ascribe to the viewpoint that severe sepsis is an ICU-only condition, a myth that has been discounted by multiple studies.^{1,4,5} Although our study shows a paucity of evidence in both ICU and non-ICU-based severe sepsis, almost half of severe sepsis occurs outside the ICU, carrying with it many of the same clinical implications. Additionally, increased morbidity, mortality, and resource utilization are known to be true in all patients with severe sepsis, irrespective of where they receive treatment in the hospital.⁴⁻⁶ Recent evidence has also shown that severe sepsis treated on the floor may be clinically, epidemiologically, and even prognostically unique from its ICU counterpart.^{5,58,59} Therefore, it appears that research domains with tailored interventions to both ICU and non-ICU severe sepsis patients are important areas of inquiry for clinicians. Such research may serve the purpose of assessing impact of early mobilization and unmasking any treatment heterogeneity that may exist when dealing with severe sepsis. Though trials of PT in ICU-based severe sepsis are underway,⁶⁰ it is prudent that these also extend beyond the ICU-setting.

Third, variability in early mobility practices and billing documentation for severe sepsis patients may exist, adding barriers to performing high-quality research on this topic. In fact, administrative billing records for PT may offer insufficient granularity about services provided or therapies administered, particularly in the ICU where variability in early mobilization practices have been shown despite common employment of physiotherapists.⁶¹

Finally, many hospitalists may believe that patients with severe sepsis are simply “too sick” for early mobilization or PT, possibly limiting their participation in clinical or research-based interventions. This perception has been well described in ICU populations, where it has been well studied and shown to be false.⁴¹⁻⁴³ Nevertheless, if severe sepsis patients are viewed as relatively sick hospitalized patients, it is plausible that resistance against early mobilization interventions may exist.⁶² Understanding these biases and being mindful of such barriers when conducting studies in this area would be important.

CONCLUSION AND FUTURE DIRECTIONS

The cost burdens of severe sepsis are substantial. Elixhauser et al. suggest that it is currently the single most expensive cause of acute hospitalization in the United States.⁶³ Importantly, a large proportion of patients with severe sepsis receive care from hospitalists and/or floor teams on the general wards. Our integrative review has demonstrated a knowledge gap when it comes to rigorous assessments of PT and mobilization treatments in patients with severe sepsis within and beyond the ICU. Existing evidence provides a strong rationale for why functional decline occurs in patients with severe sepsis. A reasonable argument for PT-

based interventions to mitigate functional decline in this subset exists, but rigorous evaluation of such interventions is necessary. Physical and mobilization-based treatments are routinely available and efficacious in several other settings and populations. It could be rapidly deployed and potentially improve outcomes in those with severe sepsis. Research would be welcomed to establish optimal dosing, efficacy, and cost effectiveness of PT and early mobilization for severe sepsis, particularly in patients treated on the general wards by hospitalists and floor teams.

How may such a research agenda be launched? A balanced multipronged approach is necessary. First, large-scale epidemiological data to understand variation in practice are needed. Focused studies carried out by community and academic hospitalists on septic patients treated outside the ICU are the call of the hour. These data, in turn, can help create registries that assess for risk factors, quality of treatment, and long-term outcomes among survivors of this condition. Second, evaluation and improvement of the coding and precision of physical and occupational therapy billing records is necessary so that their added value can be assessed and tracked using administrative data. Third, targeted prospective studies and clinical trials to directly evaluate the effect of PT in well-defined patient populations with sepsis outside the ICU are needed. In this arena, hospitalist expertise and trained physical therapists will be crucial. The focus of this work should be directed toward both short-term and long-term functional outcomes, as well as mortality and morbidity assessments. Fourth, these patient-centered efforts should loop back and inform the foundational biology of severe sepsis, thus illuminating patient-centered end points, from biomarker analysis to physiometric measurements in basic and translational research.

In conclusion, this review sheds light on the fact that interventions that may mitigate the functional and cognitive decline in survivors of severe sepsis appear underdeveloped. Although the precise benefit of such interventions remains unclear, the low-cost, widespread availability and generalizability of PT-based interventions make it a worthy candidate for future research. As the numbers of survivors of sepsis expand, an unmet public health need for interventions to improve the long-term outcomes of this population exists. Hospitalists and intensivists caring for severe sepsis patients must rise to meet this need. Together, we can help improve the lives of patients afflicted with severe sepsis, wherever they may receive care in the hospital.

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