



HHS Public Access

Author manuscript

Crit Care Clin. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Crit Care Clin. 2018 January ; 34(1): 175–188. doi:10.1016/j.ccc.2017.08.013.

Improving Long-term Outcomes after Sepsis

Hallie C. Prescott, MD, MSc¹ and Deena K. Costa, PhD, RN²

¹Department of Internal Medicine, University of Michigan; VA Center for Clinical Management Research, HSR&D Center of Innovation; 2800 Plymouth Road, North Campus Research Center, Bldg. 16, 341E, Ann Arbor, MI, USA; 734-936-5047

²Department of Systems, Populations & Leadership, School of Nursing, University of Michigan, 400 North Ingalls St #4351, Ann Arbor MI, USA, 734.764.2818

Synopsis

While acute survival from sepsis has improved dramatically in recent years, a large fraction of sepsis survivors experience poor long-term outcomes. In particular, sepsis survivors have high rates of weakness, cognitive impairment, hospital readmission, and late death. To improve long-term outcomes, in-hospital care should focus on early, effective treatment of sepsis; minimization of delirium, distress, and immobility; and preparing patients for hospital discharge. In the post-hospital setting, medical care should focus on addressing new disability and preventing medical deterioration, providing a sustained period out of the hospital to allow for recovery.

Keywords

cognitive impairment; physical disability; re-hospitalization; anxiety; depression; stress

INTRODUCTION

Short-term survival from sepsis has improved dramatically in recent years^{1,2}. As a result, there is a growing population of sepsis survivors³. These patients frequently experience new symptoms, long-term disability⁴, worsening of chronic health conditions, and increased risk for death following sepsis hospitalization⁵. In light of these poor outcomes, the Society for Critical Care Medicine has defined “post-intensive care syndrome” as new or worsening cognitive, physical, and mental health impairments that persist beyond acute hospitalization⁶. Sepsis survivors are at particularly high risk for this syndrome.

Elderly sepsis survivors experience a 10% absolute increase in moderate-to-severe cognitive impairment relative to their own pre-sepsis rates⁷, and middle-aged adult patients fare

Correspondence: Hallie C. Prescott, MD, MSc, 2800 Plymouth Road, North Campus Research Center, Bldg. 16, 341E, Ann Arbor, MI 48109-2800, Phone: 734-936-5047, Fax: 734-764-4556, hprescot@med.umich.edu.

Disclosures: This work does not represent the position or policy of the US government of the Department of Veteran’s Affairs. The authors have no financial conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

similarly⁸. Elderly patients also develop an average one to two new limitations of activities of daily living (e.g. dressing, bathing) and instrumental activities of daily living (e.g. taking medications, managing money) around the time of sepsis hospitalization⁷. Rates of anxiety, depression, and post-traumatic stress disorder are higher than population norms^{9–11}. For these reasons, sepsis hospitalization often represents a pivotal downturn in patients' ability to function independently¹².

These new disabilities after sepsis represent a significant public health burden, with an estimated 500,000 older sepsis survivors with functional impairments in the United States and 100,00 with moderate-severe cognitive impairment¹³. More than one in four older survivors is discharged to a post-acute care facility¹⁴. Around 40% are readmitted to the hospital at least once in the next 90 days¹⁵. One in five survivors has a late death that is not explained by pre-sepsis health status⁵.

Not all sepsis survivors experience poor long-term outcomes. Of patients surviving hospitalization, about one-third die during the following year^{14,16}, one-sixth experience severe persistent impairments, and one-half have a good recovery. The severity of impairments immediately after hospitalization do not correlate well with later outcomes¹⁷ since patients have different trajectories (e.g. progressive decline versus recovery) after sepsis¹⁸. While there are no routinely used tools to predict long-term disability after sepsis, several factors have been associated with worse outcomes (Box 1).

Box 1

Risk Factors associated with poor long-term functional outcomes

- Burden of chronic health conditions⁸²
- Duration of delirium during hospitalization⁸³
- Hearing impairment⁸⁴
- Immobility
- Frailty⁸⁵
- No spouse⁸²
- Older age
- Pre-morbid disability⁸⁶
- Prior nursing home care
- Severity of acute illness⁸²
- Vision impairment⁸⁴

While the long-term burdens of sepsis survivorship are increasingly recognized, the best in-ICU, in-hospital, and post-discharge practices for improving long-term outcomes after sepsis are still evolving. In this chapter, we review the available evidence on management strategies to improve long-term outcomes after sepsis hospitalization.

MANAGEMENT GOALS

In the ICU

Delirium¹⁹, acute distress²⁰, and immobility have each been identified as a key in-ICU factor that is associated with long-term cognitive impairment and physical disability^{21,22}. Thus, in addition to rapid treatment of infection and support for vital organs, the ICU treatment of septic patients should focus on limiting exposure to these risk factors. One evidence-based approach is the “ABCDEF” bundle²³. This is a collection of multi-disciplinary practices for mechanically ventilated patients (Box 2) that is designed to improve long-term outcomes by minimizing exposure to delirium, distress, and immobility. Aspects of the ABCDEF bundle, in its entirety or paired bundled components, have been shown to double the odds of walking and halving the odds of delirium, without a subsequent increased risk for self-extubation or reintubation^{24,25}. Newer evidence further suggests the ABCDEF bundle as newly conceptualized²³, when implemented effectively, is associated with more days alive, free of delirium and coma for patients cared for in 7 community hospitals in California²⁶.

Box 2

ABCDEF bundle and selected evidence in support of each bundle element

Bundle Element		Evidence
A	Assess, Prevent, and Manage Pain	Pain is a common memory of ICU survivors ⁸⁶⁸⁷ and increases risk for post-traumatic stress disorder ^{19,20} . When pain is routinely assessed using a validated pain scale and controlled with intravenous narcotics, sedation can often be avoided ⁸⁷⁸⁸⁴⁰ .
B	Both Spontaneous Awakening and Spontaneous Breathing Trials	Spontaneous awakening and breathing trials are associated with shorter duration of mechanical ventilation, better psychological outcomes, and significantly improved 1-year mortality ^{66,67,68} .
C	Choice of Analgesia and Sedation	Non-benzodiazepine sedatives are associated with less delirium ⁸⁸⁸⁹ , particularly in septic patients. In general, patients do better with less sedation ⁸⁹⁹⁰ . Less sedation may be achieved by spontaneous awakening trials, bolus versus continuous sedation, and targeting a lighter depth of sedation ⁸⁹⁹⁰ .
D	Delirium Monitoring and Management	Delirium is associated with greater mortality and cognitive impairment ^{9019,91} . Screening for delirium with tools such as the Confusion Assessment Method for the ICU (CAM-ICU) can increase recognition of delirium ⁹¹⁹² , prompting clinicians to address driving factors such as medications, environment and medical conditions.
E	Early Mobility and Exercise	Skeletal muscle wasting begins within 24 hours of critical illness ⁵⁶⁵⁷ . Early mobility, including walking patients during invasive mechanical ventilation, has been shown to be safe and effective at reducing short-term physical disability associated with critical illness, as well as at reducing delirium ^{5354,5455} .
F	Family Engagement and Empowerment	Families are important supports for patients’ recovery, also experience poor outcomes related to ICU care ⁶²⁶³ . Family presence on ICU rounds and open visiting hours are associated with improved satisfaction and communication ^{65 65,66} .

In the Hospital

Patients’ risk for poor long-term outcomes does not end upon ICU discharge. Medical care on the ward should focus on increasing mobility, preparing patients and caretakers both medically and emotionally for hospital discharge, and determining the most appropriate

discharge location. Patients frequently experience muscle wasting, weakness, and dysphagia after critical illness²⁷. Evaluation by physical therapists and occupational therapist can be helpful to determine whether patients require additional inpatient rehabilitation or home therapy, while evaluation by speech language pathologists is important to determine whether patients require dietary modification (e.g. pureed foods, thickened liquids) or *nil per os* precautions.

At present, issues of survivorship are rarely discussed during hospitalization²⁸. Many patients are unaware of their sepsis diagnosis²⁹, and even fewer are aware of the potential long-term sequelae. Ideally, this education regarding survivorship concerns should begin in the hospital and continue in the post-discharge setting. Fortunately, there are now many online resources where patients and families can learn about sequelae of sepsis and critical illnesses (Box 3).

Box 3

Selected Online Resources for Sepsis Survivorship

Website	Selected information available at the site
www.sepsisalliance.org	<ul style="list-style-type: none"> • signs/symptoms of sepsis • description of common sequelae • over 400 “Faces of Sepsis” – written tributes to lost loved ones and stories of survivors
www.mycicare.org/thrive	<ul style="list-style-type: none"> • several white-board videos for patient an families, including videos on preparing for hospital discharge after critical illness, post- intensive care syndrome, and wellness after critical illness • information on virtual and in-person peer support groups for critical illness survivors
www.icusteps.org	<ul style="list-style-type: none"> • information on in-person support groups in the United Kingdom • informational pamphlets for patients and families, including a guide to the ICU
www.healthtalk.org	<ul style="list-style-type: none"> • video interviews describing patient and family experiences of the ICU
www.icudelirium.org/patients	<ul style="list-style-type: none"> • information about common sequelae of critical illness, including patient testimonials • information about the Vanderbilt ICU recovery center

After Discharge

Management of sepsis survivors in the early post-hospital period should focus on ongoing rehabilitation, adaptation to functional impairments, emotional support for patients and caretakers, and active surveillance and prevention of further medical deterioration. Given the high rate of death⁵, disability⁷, and healthcare utilization¹⁴ in sepsis survivors, it is also important to discuss overall goals of care. Patients with pre-sepsis disability and further decline following sepsis hospitalization may be interested in transitioning to a palliative

focus. But, despite reduced quality of life relative to age-matched population norms^{30,31}, long-term sepsis survivors are often satisfied with their QOL and would undergo ICU treatment again³²—so patient-specific conversation is needed.

PHARMACOLOGIC STRATEGIES

Treatment of Sepsis

We recommend rapid treatment with broad spectrum antibiotics, fluid resuscitation, source control, and vasopressors, in accordance with the Surviving Sepsis Campaign³³ guidelines. We support shorter antibiotic courses for patients with rapid clinical resolution and/or improved procalcitonin level in order to minimize microbiome disruption, which in turn increases patients' risk for recurrent sepsis³⁴. Using procalcitonin to tailor antibiotics duration results in less antibiotic exposure, without increased short-term mortality. In observational studies, increased antibiotic exposure (both the duration of treatment and the number of drug classes) is independently associated with increased risk of recurrent sepsis³⁵. So, shortened antibiotic courses may also decrease patients' risk for recurrent sepsis, which is the most common reason for hospital readmission in this population. Because exposure to an increased number of drug classes is also associated with increased risk for subsequent sepsis, it is worthwhile to consider (and attempt to avoid) exposure to additional drug classes during the process of antibiotic de-escalation.

Stress-ulcer prophylaxis

Stress ulcer prophylaxis is widespread in the ICU, but risk of bleeding is low, and concentrated among patients with coagulopathy or respiratory failure³⁶. Thus, we do not recommend stress-ulcer prophylaxis in patients without either of these risk factors, as maintaining acidic gastric acid is a protective factor against infection. Indeed, stress ulcer prophylaxis, in particular proton pump therapy, has been associated with increased risk for *c. difficile* infection and pneumonia³⁷. When stress ulcer prophylaxis is indicated (for respiratory failure or coagulopathy), we recommend H2 receptor agonists over proton pump inhibitors, in order to minimize risk for subsequent infection.

Pharmacological Management of Pain and Agitation

Patients frequently experience pain and discomfort during the ICU. Patients were traditionally treated with deep sedation while mechanically ventilated, but this practice has been associated with longer duration of mechanical ventilation, higher rates of delirium, poor long-term cognitive function, and higher long-term mortality^{38,39}. Thus, the current standard as described in the *Pain, Agitation, and Delirium* guidelines (and supported by the Surviving Sepsis Campaign Guidelines³³) is to use “lighter” sedation⁴⁰. This can be achieved by a variety of strategies, including treating pain first in conjunction with routine pain assessments using a validated pain assessment scale (and thereby limiting need for sedation); using intermittent rather than continuous sedation medications; using a sedation scale (e.g. Richmond Agitation Sedation Scale) to target light levels of continuous sedation; and performing daily awakening trials during which continuous sedative medications are turned off and restarted only if needed⁴⁰.

Beyond treating pain and targeting light sedation, the choice of sedative agent is also important. Benzodiazepines have been associated with increased risk for delirium, which is in turn associated with worse long-term outcomes. Propofol and dexmedetomidine are short-acting continuous sedative medications that are preferred over benzodiazepines for patients requiring continuous sedation.

Medications associated with ICU-acquired weakness

Observational studies suggest that several medications (e.g. corticosteroids, aminoglycosides, and in particular neuromuscular blocking agents (NMB)) may exacerbate ICU-acquired weakness through direct toxicity to nerves, muscles, or both. However, the quality of this data is low due to confounding by indication and other methodological limitations⁴¹. At present, the Surviving Sepsis Campaign guidelines have a weak recommendation for using 48 hours of NMB in patients with sepsis-induced ARDS and $\text{PaO}_2/\text{FIO}_2 < 150$ based on a 340-person, multi-center RCT showing a mortality benefit^{33,42}. In this study, there was no increase in ICU-acquired weakness in the NMB arm, but all patients were deeply sedated, half of the control arm received at least one dose of NMB, and there was no long-term follow-up of weakness. Thus, considerable equipoise remains, and uptake of NMB has been low⁴³. While we await further RCT data on the safety and efficacy of NMB from the ongoing Reevaluation of Systemic Early Neuromuscular Blockade Trial (ROSE)⁴⁴, we prefer to reserve NMB for only the sickest patients with sepsis-related ARDS (e.g. those with $\text{PaO}_2/\text{FIO}_2 < 75$).

Medication Reconciliation and Titration

Medication reconciliation at the time of hospital discharge is particularly important for sepsis patients, who are likely to have had multiple medication adjustments during their hospitalization⁴⁵. Chronic medications are frequently held and forgotten, while medications to treat acute symptoms may be continued inadvertently^{46–48}. In a recent prospective study, 24% of patients who were prescribed an atypical antipsychotic for acute delirium during critical illness had the medication continued at discharge—despite a black-box warning for long-term use and scant evidence that atypical antipsychotics are helpful for acute symptoms⁴⁹. Beyond getting the medication list correct, it is important to consider that the dosages of chronic medications may need to be adjusted as a result of physiologic changes during sepsis hospitalization (e.g. reduced muscle mass or decline in glomerular filtration rate).

NON-PHARMACOLOGIC STRATEGIES

ICU Diaries

ICU diaries are written accounts of a patient's hospitalization, typically created by bedside nurses and family members. They describe the hospital course in lay terms and often include drawings or photographs, helping patients to understand what transpired while they were sedated. Providing a diary at one month is associated with lower rates of PTSD in patients and relatives at 3 months^{50,51}. While diaries are provided by many hospitals in Scandinavia and western Europe⁵², they are rarely used in the United States. Describing the hospital

course in simple terms may provide similar benefit, and is commonly included in many ICU follow-up clinics⁵³.

Early Activity and Mobility

Early mobility, including progressively increasing a patient's activity level to the goal of ambulation during invasive mechanical ventilation, has been shown to be safe and effective at reducing short-term physical disability associated with critical illness, as well as at reducing delirium^{54,55}. Patients randomized to early mobility interventions have better physical function at ICU and hospital discharge. They may also more likely to be discharged directly home (43% versus 24% discharged to home, $p=0.06$)⁵⁴. While early mobility interventions have not been shown to improve long-term physical function, skeletal muscle weakness has been associated with both early and late mortality after critical illness⁵⁶. Thus, it is reasonable to suspect that the improvements in functional status at discharge do indeed translate to better long-term outcomes.

It is important to note that the main benefit of mobility interventions seems to be the prevention of acute muscle loss. Skeletal muscle wasting begins within 24 hours of critical illness⁵⁷, so mobility interventions must occur as soon as possible. Interventions that begin later in the ICU stay⁵⁸, after ICU discharge⁵⁹, or after hospital discharge⁶⁰ have generally not been successful.

Cognitive Therapy

In a single-center pilot feasibility study, ICU survivors randomized to cognitive and physical rehabilitation showed improved executive functioning by three months⁶¹. However, another single-center pilot study testing a multi-faceted intervention including early cognitive therapy delivered twice a day during the ICU found no difference in cognitive function at three months⁶². Larger studies are needed to assess early and later cognitive therapy.

Family Engagement

Family engagement has been recognized as an increasingly important goal in ICU care for several reasons. First, family members often serve as surrogate decision-makers when patients are unable to voice their own wishes. Second, families provide invaluable support during a patient's recovery. With increasing fragmentation of healthcare delivery, family members may be the only people capable of placing the sepsis hospitalization within the broader context of a patient's overall recovery. Third, critical illness has a profound effect on families, many of whom experience stress and depression as a result of their caregiving or surrogate decision-maker role^{29,63}. Effective family engagement includes showing respect for family's values and goals, sharing information on a patient's status in a timely fashion, and actively partnering with families to develop treatment plans⁶⁴. Family presence on ICU rounds and open visiting hours are increasingly accepted ways to incorporate families into ICU care^{65,66}.

ICU Follow-up Clinics

Specialized post-ICU clinics have been proposed as a strategy for improving long-term outcomes after critical illness⁵³. These clinics are common in the United Kingdom, where

approximately one third of intensive care units run a follow-up clinic⁶⁷. Over the past few years, there has also been growing interest in ICU follow-up clinics within the United States. The first centers were the Critical Care Recovery Center at Indiana University and the Vanderbilt ICU Recovery Center⁶⁸, and several additional centers are now building similar clinics. The exact organization of these clinics varies across centers, and no optimal model has been identified⁶⁷.

The evidence in support of ICU follow-up clinics is limited. The largest study to date evaluated the impact of a self-directed physical therapy program and visits to a nurseled follow-up clinic at 3 and 9 months⁵³. During the clinic visit, patients had a medication review, discussion of their ICU course, physiological screen, evaluation for specialty referral, a visit to their ICU, and a formal letter to their primary care physician. There was no improvement in QOL, PTSD, depression, costs, or mortality among patients randomized to the intervention⁵³. There are several possible explanations for this negative trial. The trial enrolled unselected ICU survivors, did not formally integrate families into the intervention, and did not see patients in clinic until 3 months after ICU discharge. Furthermore, the medical complexity of ICU survivors may require an interdisciplinary approach, as is used in many ICU follow-clinics⁶⁸.

SELF-MANAGEMENT STRATEGIES

Symptom Management

Patients often experience anxiety, fear, and agitation during ICU stays, but sedative medications commonly used to treat these symptoms are associated with worse long-term outcomes, particularly when given in high doses. There is a growing body of literature supporting patient-controlled symptom management as an adjunct or replacement to nurse-administered sedation. For example, in a 373-person RCT, patient-directed music therapy resulted in reduced anxiety and reduced sedative dosing compared to usual care or noise-cancelling headphones⁶⁹. A current RCT is testing whether patient-controlled sedative therapy with dexmedetomidine is safe and effective compared to nurse-administered sedation⁷⁰.

Exercise and Rehabilitation

Evidence for self-directed rehabilitation is mixed. In a study of 126 ICU patients, randomization to receiving a 6-week rehabilitation manual was associated with improved physical function at 8 weeks and 6 months⁷¹. However, in a study of 286 ICU patients randomized to a 3-month rehabilitation manual coupled with referral to a nurse-run ICU follow-up clinic showed no improvement in physical function at 6 months or 1 year. It is possible that the benefit of self-directed rehabilitation does not persist more than a few months. In older patients recently discharged from the hospital, self-directed exercise programs have been associated with greater mobility, but also with an increased number of falls—suggesting that self-directed rehabilitation programs are not without risk.

Peer-to-Peer Support

There is a long tradition of peer support groups for chronic conditions such as cancer, diabetes, mental health and substance disorders. Recently, peer support groups have also been formed for critical illness survivors and families, such as ICUSteps⁷² in the United Kingdom and Society for Critical Care Medicine's Thrive Network⁷³ in the United States. In these support groups, critical illness survivors share their experiences, provide empathy, and give and receive practical advice on navigating life with new disabilities⁷⁴. Patients and caretakers benefit from giving and receiving support⁷⁴. These groups may also serve as a venue to discuss the role of religion and spirituality in recovery, which are often neglected clinicians⁷⁴. While the peer-support model is appealing, the optimal structure and process of these groups has yet to be determined.

EVALUATION, ADJUSTMENT, RECURRENCE

Evaluation

Sepsis survivors are at high risk for further medical deterioration in the weeks to months following hospital discharge. By three months, over 40% of older survivors are readmitted to the hospital at least once^{15,75}. Many of these readmissions are for potentially preventable causes—most commonly infection, heart failure exacerbation, acute renal failure, chronic obstructive pulmonary disease exacerbation, and aspiration pneumonia¹⁵. Thus, in addition to addressing new disabilities, early outpatient care should focus on active screening for and mitigating risk of these common problems.

Adjustment

As a result of impaired mobility, many patients are unable to continue previous activities and hobbies. Patients may be newly dependent on spouses and family members to complete activities of daily living, such as bathing and dressing. Because of this loss of independence, patients may feel helpless, embarrassed, or angry²⁹. Family members also experience significant life changes following a loved one's sepsis hospitalization. Family members have new or growing responsibilities as a caretaker, and completing domestic chores that the patient can no longer complete²⁹. These new responsibilities coupled with the stress of the patient's illness may lead family members to feel frustration, guilt, anxiety, stress, and depression^{29,63}. Beyond recognizing and validating patients' and family's experiences and emotion, clinicians should refer interested patients and families to peer-to-peer support groups and online resources (Box 3) where they can learn more about survivorship issues.

Recurrence

The most common cause of hospital readmission in sepsis survivors is infection. A full 6% of older Americans who survive a sepsis hospitalization return to the hospital within three months for another bout of sepsis—while nearly a quarter return for some sort of infection¹⁵. However, on closer review of these readmissions (not merely examining the principal diagnosis codes), as many as one-half to two-thirds of all readmissions appear to be infection-related^{16,76,77,78}. There is an even split between new infections and relapsed/recurrent infections⁷⁶—suggesting that these readmissions are not merely treatment failures.

There are many reasons for which sepsis survivors are at high risk for subsequent infection. First, the demographic and health factors that placed patients at risk for their first episode of sepsis are often still present. Second, sepsis is often followed by a period of relative immune-suppression, during which time patients are at heightened risk for subsequent infections^{79,80}. Third, as a result of both infection and its treatment, patients experience microbiome disruption, which may further increase risk for subsequent sepsis^{34,81}.

Beyond standard infection-prevention measures (hand-washing, avoidance of sick contacts, keeping vaccines up to date), there are no specific therapies to boost patients' immune system after sepsis. In the future, immune-therapy may be used to restore immune function, while diet and probiotics may be used to restore the gut microbiome⁷⁸.

SUMMARY

While acute survival from sepsis has improved dramatically in recent years, a large fraction of sepsis survivors experience poor long-term outcomes. In particular, sepsis survivors have high rates of weakness, cognitive impairment, hospital readmission, and late death. To improve long-term outcomes, in-hospital care should focus on early, effective treatment of sepsis; minimization of delirium, distress, and immobility; and preparing patients for hospital discharge. In the post-hospital setting, medical care should focus on addressing new disability and preventing medical deterioration, providing a sustained period out of the hospital to allow for recovery.

Acknowledgments

Funding: This work was supported by grants K08 GM115859 [HCP] from the National Institute of General Medical Sciences of the National Institutes of Health and K08 HS024552 [DKC] from the Agency for Healthcare Research and Quality.

References

1. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA*. 2014; 311:1308–1316. [PubMed: 24638143]
2. Prescott HC, Kepreos KM, Wiitala WL, Iwashyna TJ. Temporal Changes in the Influence of Hospitals and Regional Healthcare Networks on Severe Sepsis Mortality. *Crit Care Med*. 2015; 43:1368–1374. [PubMed: 25803652]
3. Iwashyna TJ, Speelman EC. Advancing a Third Revolution in Critical Care. *Am J Respir Crit Care Med*. 2016; 194:782–783. [PubMed: 27689702]
4. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010; 304:1787–1794. [PubMed: 20978258]
5. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. *BMJ*. 2016; 353:i2375–i2375. [PubMed: 27189000]
6. Needham DM, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012; 40:502–509. [PubMed: 21946660]
7. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010; 304:1787–1794. [PubMed: 20978258]
8. Pandharipande PP, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013; 369:1306–1316. [PubMed: 24088092]

9. Parker AM, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med.* 2015; 43:1121–1129. [PubMed: 25654178]
10. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, Needham DM. Depression in general intensive care unit survivors: a systematic review. *Intensive Care Med.* 2009; 35:796–809. [PubMed: 19165464]
11. Nikayin S, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry.* 43:23–29.
12. Angus DC. The lingering consequences of sepsis: a hidden public health disaster? *JAMA.* 2010; 304:1833–1834. [PubMed: 20978262]
13. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc.* 2012; 60:1070–1077. [PubMed: 22642542]
14. Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ. Increased 1-year healthcare use in survivors of severe sepsis. *Am J Respir Crit Care Med.* 2014; 190:62–69. [PubMed: 24872085]
15. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA.* 2015; 313:1055–1057. [PubMed: 25756444]
16. Prescott HC. Variation in Postsepsis Readmission Patterns: A Cohort Study of Veterans Affairs Beneficiaries. *Ann Am Thorac Soc.* 2017; 14:230–237. [PubMed: 27854510]
17. Woon FL, Dunn CB, Hopkins RO. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. *Am J Respir Crit Care Med.* 2012; 186:333–340. [PubMed: 22700858]
18. Iwashyna TJ. Trajectories of Recovery and Dysfunction after Acute Illness, with Implications for Clinical Trial Design. *Am J Respir Crit Care Med.* 2012; 186:302–304. [PubMed: 22896591]
19. Girard TD, et al. Delirium as a Predictor of Long-Term Cognitive Impairment in Survivors of Critical Illness. *Crit Care Med.* 2010; 38:1513–1520. [PubMed: 20473145]
20. Davydow DS, Zatzick D, Hough CL, Katon WJ. In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission. *Ann Am Thorac Soc.* 2013; 10:450–457. [PubMed: 23987665]
21. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the ‘ABCDE’ approach. *Curr Opin Crit Care.* 2011; 17:43–49. [PubMed: 21169829]
22. Brummel NE, et al. Understanding and reducing disability in older adults following critical illness. *Crit Care Med.* 2015; 43:1265–1275. [PubMed: 25756418]
23. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF Bundle in Critical Care. *Crit Care Clin.* 2017; 33:225–243. [PubMed: 28284292]
24. Girard TD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008; 371:126–134. [PubMed: 18191684]
25. Balas MC, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Crit Care Med.* 2014; 42:1024–1036. [PubMed: 24394627]
26. Barnes-Daly MA, Phillips G, Ely EW. Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. *Crit Care Med.* 2017; 45:171–178. [PubMed: 27861180]
27. Zielske J, Bohne S, Brunkhorst FM, Axer H, Guntinas-Lichius O. Acute and long-term dysphagia in critically ill patients with severe sepsis: results of a prospective controlled observational study. *Eur Arch Otorhinolaryngol.* 2014; doi: 10.1007/s00405-014-3148-6
28. Govindan S, Iwashyna TJ, Watson SR, Hyzy RC, Miller MA. Issues of survivorship are rarely addressed during intensive care unit stays. Baseline results from a statewide quality improvement collaborative. *Ann Am Thorac Soc.* 2014; 11:587–591. [PubMed: 24605936]
29. Gallop KH, et al. A qualitative investigation of patients’ and caregivers’ experiences of severe sepsis*. *Crit Care Med.* 2015; 43:296–307. [PubMed: 25251757]
30. Winters BD, et al. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med.* 2010; 38:1276–1283. [PubMed: 20308885]
31. Yende S, et al. Long-Term Quality of Life Among Survivors of Severe Sepsis. *Crit Care Med.* 2016; 44:1461–1467. [PubMed: 26992066]

32. Cuthbertson BH, et al. Mortality and quality of life in the five years after severe sepsis. *Crit Care Lond Engl*. 2013; 17:R70.
33. Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017; doi: 10.1007/s00134-017-4683-6
34. Prescott HC, Dickson RP, Rogers MA, Langa KM, Iwashyna TJ. Hospitalization Type and Subsequent Severe Sepsis. *Am J Respir Crit Care Med*. 2015; 192:581–588. [PubMed: 26016947]
35. Baggs J. Increased Risk of Sepsis during Hospital Readmission Following Exposure to Certain Antibiotics during Hospitalization. in (Idsa, 2016).
36. Cook DJ, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med*. 1994; 330:377–381. [PubMed: 8284001]
37. Krag M, Perner A, Møller MH. Stress ulcer prophylaxis in the intensive care unit. *Curr Opin Crit Care*. 2016; 22:186–190. [PubMed: 26849250]
38. Kress JP, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med*. 2003; 168:1457–1461. [PubMed: 14525802]
39. Shehabi Y, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012; 186:724–731. [PubMed: 22859526]
40. Barr J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013; 41:263–306. [PubMed: 23269131]
41. Puthuchery Z, et al. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? *Am J Respir Crit Care Med*. 2012; 185:911–917. [PubMed: 22550208]
42. Papazian L, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010; 363:1107–1116. [PubMed: 20843245]
43. Bellani G, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*. 2016; 315:788–800. [PubMed: 26903337]
44. Huang DT, et al. Design and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade Trial for Acute Respiratory Distress Syndrome. *Ann Am Thorac Soc*. 2017; 14:124–133. [PubMed: 27779896]
45. Stollings JL, et al. Medication Management to Ameliorate Post-Intensive Care Syndrome. *AACN Adv Crit Care*. 2016; 27:133–140. [PubMed: 27153300]
46. Bell CM, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA*. 2011; 306:840–847. [PubMed: 21862745]
47. Morandi A, et al. Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. *J Am Geriatr Soc*. 2013; 61:1128–34. [PubMed: 23855843]
48. Scales DC, et al. Unintentional Continuation of Medications Intended for Acute Illness After Hospital Discharge: A Population-Based Cohort Study. *J Gen Intern Med*. 2016; 31:196–202. [PubMed: 26369941]
49. Tomichek JE, et al. Antipsychotic prescribing patterns during and after critical illness: a prospective cohort study. *Crit Care Lond Engl*. 2016; 20:378.
50. Jones C, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care*. 2010; 14:R168–R168. [PubMed: 20843344]
51. Jones C, Bäckman C, Griffiths RD. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: a pilot study. *Am J Crit Care Off Publ Am Assoc Crit -Care Nurses*. 2012; 21:172–176.
52. [Accessed: 12th April 2017] ICU-diary.org. Available at: <http://www.icu-diary.org/diary/start.html>
53. Cuthbertson BH, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ*. 2009; 339:b3723–b3723. [PubMed: 19837741]
54. Schweickert WD, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009; 373:1874–1882. [PubMed: 19446324]

55. Schaller SJ, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet Lond Engl*. 2016; 388:1377–1388.
56. Puthuchery Z, Prescott H. Skeletal Muscle Weakness Is Associated With Both Early and Late Mortality After Acute Respiratory Distress Syndrome. *Crit Care Med*. 2017; 45:563–565. [PubMed: 28212226]
57. Puthuchery ZA, et al. Acute Skeletal Muscle Wasting in Critical Illness. *JAMA*. 2013; 310:1591–1591. [PubMed: 24108501]
58. Moss M, et al. A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med*. 2016; 193:1101–1110. [PubMed: 26651376]
59. Walsh TS, et al. Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge: The RECOVER Randomized Clinical Trial. *JAMA Intern Med*. 2015; 175:901–910. [PubMed: 25867659]
60. Connolly, B., et al. *Cochrane Database of Systematic Reviews*. Connolly, B., editor. John Wiley & Sons, Ltd; 2015. p. CD008632-CD008632.
61. Jackson JC, et al. Cognitive and physical rehabilitation of intensive care unit survivors. *Crit Care Med*. 2012; 40:1088–1097. [PubMed: 22080631]
62. Brummel NE, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med*. 2014; 40:370–379. [PubMed: 24257969]
63. Cameron JI, et al. One-Year Outcomes in Caregivers of Critically Ill Patients. *N Engl J Med*. 2016; 374:1831–41. [PubMed: 27168433]
64. Brown SM, et al. Defining patient and family engagement in the intensive care unit. *Am J Respir Crit Care Med*. 2015; 191:358–360. [PubMed: 25635496]
65. Davidson JE. Family presence on rounds in neonatal, pediatric, and adult intensive care units. *Ann Am Thorac Soc*. 2013; 10:152–156. [PubMed: 23607848]
66. Chapman DK, et al. Satisfaction With Elimination of all Visitation Restrictions in a Mixed-Profile Intensive Care Unit. *Am J Crit Care Off Publ Am Assoc Crit -Care Nurses*. 2016; 25:46–50.
67. Griffiths JA, Barber VS, Cuthbertson BH, Young JD. A national survey of intensive care follow-up clinics. *Anaesthesia*. 2006; 61:950–955. [PubMed: 16978309]
68. Huggins EL, et al. A Clinic Model: Post-Intensive Care Syndrome and Post-Intensive Care Syndrome-Family. *AACN Adv Crit Care*. 2016; 27:204–211. [PubMed: 27153309]
69. Chlan LL, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. *JAMA*. 2013; 309:2335–2344. [PubMed: 23689789]
70. [Accessed: 13th April 2017] Project Information - NIH RePORTER - EFFICACY OF SELF-MANAGEMENT OF SEDATIVE THERAPY BY VENTILATED ICU PATIENTS. Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=9263829&icde=33867669&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pb all=
71. Jones C, et al. Rehabilitation after critical illness: A randomized, controlled trial. *Crit Care Med*. 2003; 31:2456–2461. [PubMed: 14530751]
72. [Accessed: 13th April 2017] Welcome - ICUsteps. Available at: <http://www.icusteps.org/>
73. [Accessed: 11th April 2017] Patients and Families | SCCM | Connect With Patients and Families. Available at: <http://www.myicucare.org/Thrive/Pages/Find-In-Person-Support-Groups.aspx>
74. Mikkelsen ME, et al. Peer Support as a Novel Strategy to Mitigate Post-Intensive Care Syndrome. *AACN Adv Crit Care*. 2016; 27:221–9. [PubMed: 27153311]
75. Liu V, et al. Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med*. 2014; 9:502–507. [PubMed: 24700730]
76. Sun A, et al. Association between Index Hospitalization and Hospital Readmission in Sepsis Survivors. *Crit Care Med*. 2015

77. Donnelly JP, Hohmann SF, Wang HE. Unplanned Readmissions After Hospitalization for Severe Sepsis at Academic Medical Center-Affiliated Hospitals. *Crit Care Med.* 2015; doi: 10.1097/CCM.0000000000001147
78. Prescott HC. Toward a Nuanced Understanding of the Role of Infection in Readmissions After Sepsis. *Crit Care Med.* 2016; 44:634–5. [PubMed: 26901548]
79. Boomer JS, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA.* 2011; 306:2594–2605. [PubMed: 22187279]
80. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis.* 2013; 13:260–8. [PubMed: 23427891]
81. Zaborin A, et al. Membership and behavior of ultra-low-diversity pathogen communities present in the gut of humans during prolonged critical illness. *MBio.* 2014; 5:e01361–14. [PubMed: 25249279]
82. Heyland DK, et al. Predicting Performance Status 1 Year After Critical Illness in Patients 80 Years or Older. *Crit Care Med.* 2016; 44:1718–1726. [PubMed: 27075141]
83. Brummel NE, et al. Delirium in the ICU and Subsequent Long-Term Disability Among Survivors of Mechanical Ventilation*. *Crit Care Med.* 2014; 42:369–377. [PubMed: 24158172]
84. Ferrante LE, et al. Factors Associated with Functional Recovery among Older Intensive Care Unit Survivors. *Am J Respir Crit Care Med.* 2016; 194:299–307. [PubMed: 26840348]
85. Brummel NE, et al. Frailty and Subsequent Disability and Mortality Among Patients With Critical Illness. *Am J Respir Crit Care Med.* 2016; doi: 10.1164/rccm.201605-0939OC
86. Ferrante LE, et al. Functional trajectories among older persons before and after critical illness. *JAMA Intern Med.* 2015; 175:523–529. [PubMed: 25665067]
87. Stein-Parbury J, McKinley S. Patients' experiences of being in an intensive care unit: a select literature review. *Am J Crit Care Off Publ Am Assoc Crit -Care Nurses.* 2000; 9:20–27.
88. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet.* 2010; 375:475–480. [PubMed: 20116842]
89. Riker RR, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009; 301:489–499. [PubMed: 19188334]
90. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med.* 2014; 370:444–454. [PubMed: 24476433]
91. Ely EW, et al. Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit. *JAMA.* 2004; 291:1753–1753. [PubMed: 15082703]
92. van Eijk MMJ, et al. Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med.* 2009; 37:1881–1885. [PubMed: 19384206]

Key Points

- Acute survival from sepsis has improved dramatically in recent years, resulting in a large population of sepsis survivors
- Many sepsis survivors experience long-term sequelae of sepsis, including weakness, cognitive impairment, frequent hospital readmission, and increased risk for death
- In-hospital care should focus on treatment of sepsis; minimizing exposure to delirium, distress, and immobility; and preparing patients and families both emotionally and physically for hospital discharge
- Post-hospital care should focus on validating a patients' experience, referral to appropriate therapies (e.g. physical or speech therapy), and actively screening for and preventing medical deterioration