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Author manuscript

JAMA. Author manuscript; available in PMC 2019 January 02.

Published in final edited form as:

JAMA. 2018 January 02; 319(1): 62–75. doi:10.1001/jama.2017.17687.

## Enhancing Recovery From Sepsis:

### A Review

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### Abstract

**IMPORTANCE**—Survival from sepsis has improved in recent years, resulting in an increasing number of patients who have survived sepsis treatment. Current sepsis guidelines do not provide guidance on posthospital care or recovery.

**OBSERVATIONS**—Each year, more than 19 million individuals develop sepsis, defined as a life-threatening acute organ dysfunction secondary to infection. Approximately 14 million survive to hospital discharge and their prognosis varies. Half of patients recover, one-third die during the following year, and one-sixth have severe persistent impairments. Impairments include development of an average of 1 to 2 new functional limitations (eg, inability to bathe or dress independently), a 3-fold increase in prevalence of moderate to severe cognitive impairment (from 6.1% before hospitalization to 16.7% after hospitalization), and a high prevalence of mental health problems, including anxiety (32% of patients who survive), depression (29%), or posttraumatic stress disorder (44%). About 40% of patients are rehospitalized within 90 days of discharge, often for conditions that are potentially treatable in the outpatient setting, such as infection (11.9%) and exacerbation of heart failure (5.5%). Compared with patients hospitalized for other diagnoses, those who survive sepsis (11.9%) are at increased risk of recurrent infection than matched patients (8.0%) matched patients ( $P < .001$ ), acute renal failure (3.3% vs 1.2%,  $P < .001$ ), and new

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**Disclaimer:** The views expressed in this article do not necessarily reflect the position or policy of the US government or the Department of Veteran Affairs. Dr Angus, a JAMA associate editor, was not involved in the editorial evaluation of or decision to publish this article.

**Additional Contributions:** We thank Theodore “Jack” Iwashyna, MD, PhD, of the University of Michigan for thoughtful feedback on this review and Bronwen Connolly, MSc, PhD, MCSP, from St Thomas’ hospital in London for stimulating discussion on rehabilitation after sepsis. Neither were compensated for their contributions. We also thank the Michigan Center for Integrative Research in Critical Care.

**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Prescott reported receiving grant support from the National Institutes of Health and serving on the advisory board of a Bristol-Myers Squibb–sponsored study. Dr Angus reported that he has served as a consultant for Ferring Pharmaceuticals.

cardiovascular events (adjusted hazard ratio [HR] range, 1.1–1.4). Reasons for deterioration of health after sepsis are multifactorial and include accelerated progression of preexisting chronic conditions, residual organ damage, and impaired immune function. Characteristics associated with complications after hospital discharge for sepsis treatment are not fully understood but include both poorer presepsis health status, characteristics of the acute septic episode (eg, severity of infection, host response to infection), and quality of hospital treatment (eg, timeliness of initial sepsis care, avoidance of treatment-related harms). Although there is a paucity of clinical trial evidence to support specific postdischarge rehabilitation treatment, experts recommend referral to physical therapy to improve exercise capacity, strength, and independent completion of activities of daily living. This recommendation is supported by an observational study involving 30 000 sepsis survivors that found that referral to rehabilitation within 90 days was associated with lower risk of 10-year mortality compared with propensity-matched controls (adjusted HR, 0.94; 95% CI, 0.92–0.97,  $P < .001$ ).

**CONCLUSIONS AND RELEVANCE**—In the months after hospital discharge for sepsis, management should focus on (1) identifying new physical, mental, and cognitive problems and referring for appropriate treatment, (2) reviewing and adjusting long-term medications, and (3) evaluating for treatable conditions that commonly result in hospitalization, such as infection, heart failure, renal failure, and aspiration. For patients with poor or declining health prior to sepsis who experience further deterioration after sepsis, it may be appropriate to focus on palliation of symptoms.

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Sepsis is defined as life-threatening acute organ dysfunction secondary to infection<sup>1</sup> and affects more than 19 million people each year.<sup>2</sup> In-hospital mortality has declined,<sup>3,4</sup> from 35% in 2000 to 18% in 2012, resulting in a large number of sepsis survivors. Emerging data suggest that patients who survive sepsis frequently experience new symptoms,<sup>5</sup> long-term disability,<sup>6</sup> and worsening of chronic health conditions<sup>7,8</sup> for which they will seek care from many types of clinicians.

An international survey suggests a need for improved management after hospital discharge. Of 1475 patients who survived hospitalization for sepsis, there was only low to moderate satisfaction with support services after they were discharged.<sup>5</sup> In addition, re-hospitalization after sepsis accounts for 12.2% of all US hospital readmissions and 14.5% of readmission costs.<sup>9</sup> Therefore, improving medical care after sepsis hospitalizations may reduce health care utilization and costs. Although physical disability, cognitive impairment, and hospital readmission are common after sepsis, sepsis treatment guidelines provide no recommendations on posthospital management.<sup>10</sup> This article reviews the epidemiology, pathophysiology, and clinical sequelae in the months following hospital discharge of patients treated for sepsis. Management strategies and directions for future research are also reviewed.

## Methods

A literature search of MEDLINE was conducted in PubMed through April 26, 2017, using search terms and synonyms for *sepsis* and *survivors*. Non-English language articles or those published before January 1, 2000, were excluded. Bibliographies of retrieved studies were searched for other relevant studies. Articles were reviewed for their contribution to current

understanding of sepsis survivorship, with priority given to clinical trials, large longitudinal observational studies, and more recently published articles.

## Observations

### Epidemiology

Throughout the world, an estimated 19.4 million patients develop sepsis each year, of whom 14.1 million survive to hospital discharge.<sup>2</sup> In 2014, 1.3 million US adults survived a hospitalization for sepsis<sup>11</sup>(Figure 1), of whom 56% were aged 65 years or older.<sup>11</sup> Approximately half of patients who survive hospitalization for sepsis have a complete or near complete recovery. Overall, one-sixth experience severe persistent physical disability or cognitive impairment, and one-third die during the following year.<sup>6,12</sup> Half of deaths in the year after hospitalization for sepsis are related to complications of sepsis, while half are explained by age or preexisting comorbidities.<sup>13</sup>

### Pathophysiology

Sepsis can occur due to either community-acquired or nosocomial infection. Among 307 491 US hospitalizations for sepsis, 63% of underlying infections were community acquired, 11% were hospital acquired, and 26% were health care associated (acquired outside a hospital by patients with recent exposure to health care facilities, such as nursing home residents, hemodialysis recipients, or recently hospitalized patients).<sup>14</sup> The most common underlying infection is pneumonia (40%), followed by abdominal, genitourinary, primary bacteremia, and skin or soft tissue infections.<sup>15,16</sup>

Based on experimental and human volunteer models, sepsis was initially presumed to be an extreme, body-wide inflammatory response that led to alterations in microvascular flow, endothelial leak, and compromised parenchymal cell function, manifesting clinically as inadequate tissue perfusion and multisystem organ dysfunction. However, more recent evidence demonstrates that the pathophysiological response is more complex and variable<sup>17</sup> (Figure 2). First, the initial host response includes activation of pro-inflammatory pathways and anti-inflammatory innate immune pathways, as well as alterations in adaptive immune pathways. Second, the characteristics of immune system changes vary and depend on both host and pathogen characteristics, as well as recent medical events (eg, surgery, other infection) and treatment (eg, timing of antibiotics).<sup>17</sup> Third, the resolution of immune system changes in response to sepsis is complex and frequently prolonged. Many patients continue to have inflammatory changes, immune suppression, or both after sepsis.<sup>19</sup>

The reasons for these immune system changes are complex and include epigenetic<sup>20</sup> and metabolic<sup>21</sup> reprogramming of immune cells induced by the original septic insult and by ongoing changes in the host environment, such as neuroendocrine<sup>22</sup> or microbiome<sup>23</sup> alterations. These processes continue despite successful eradication of the initial pathogen and increase a patient's risk of secondary episodes of infection or sepsis. The combination of the initial septic insult and ongoing abnormalities in host control systems contributes to persistent organ dysfunction. The severity of immune suppression and organ dysfunction after sepsis treatment is influenced by a patient's presepsis health and by characteristics of

the infection (pathogen load, virulence), host response, and the quality of early sepsis treatment. Patients may also experience sequelae from iatrogenic complications<sup>24,25</sup> and medication errors<sup>26–28</sup> during and after hospitalization.

Recovery from sepsis also varies (Figure 2). There are no validated tools to estimate a patient's likelihood of complete recovery. However, several prognostic factors have been identified. Patients with preexisting disability, frailty, or nursing home use are less likely to regain functional independence,<sup>30–35</sup> while previously healthy patients have a higher chance of recovery. Importantly, the severity of cognitive impairments shortly after hospitalization do not predict well subsequent impairment.<sup>29</sup>

## Clinical Sequelae

### Physical Limitations

After hospitalization for sepsis, a patient's ability to function independently frequently declines. Patients treated for sepsis typically develop 1 to 2 new limitations of activities of daily living (ADLs), such as inability to manage money, bathe, or toilet independently<sup>6</sup> after hospital discharge (Table 1). The causes of functional decline are multifactorial. Patients often develop physical weakness following critical illness, which may be due to myopathy, neuropathy,<sup>40</sup> cardio-respiratory impairments, cognitive impairment, or a combination of these conditions.

Swallowing difficulty is common and may be due to muscular weakness or neurological damage. Among patients discharged from the intensive care unit (ICU), those with sepsis are more likely to have aspiration on fiberoptic endoscopic evaluation of swallowing (63% vs 23%,  $P < .01$ ) than those without sepsis.<sup>36</sup> Among older US residents who survive hospitalization for sepsis, risk of 90-day readmission for aspiration is 1.8% vs 1.2% after hospitalizations for other diagnoses ( $P = .06$ ).<sup>37</sup>

Physical function typically improves after hospital discharge. In a prospective study of functional recovery after sepsis, patients experienced clinically important improvements in 6-minute walk distance (from a mean of 45.9% of predicted distance for age at hospital discharge to a mean of 69% 3 months after discharge,  $P < .05$ ); quadriceps strength (68.5% vs 50.9%,  $P < .05$ ); and handgrip strength (68.5% vs 54.6%,  $P < .05$ ).<sup>41</sup> By 3 months after discharge, 60% of 51 patients could walk for 30 minutes per day.<sup>41</sup> However, physical function typically remained below population norms and often does not return to presepsis levels.<sup>6,41</sup>

### Cognitive Impairment

Patients may acquire neurological damage during hospitalization for sepsis through a variety of mechanisms, including cerebral ischemia, metabolic derangements, and neuroinflammation.<sup>42</sup> Patients frequently experience delirium and impaired consciousness. After hospitalization, patients may have long-term impairments in memory, attention, verbal fluency, and executive functioning.<sup>42</sup>

In an observational study of 516 US Health and Retirement Study participants who survived a hospitalization with sepsis, the prevalence of moderate to severe cognitive impairment increased from 6.1% before hospitalization to 16.7% after hospitalization.<sup>6</sup> By contrast, patients surviving hospitalization without sepsis did not have an increase in the incidence of moderate to severe impairment.<sup>6</sup> The prevalence of milder cognitive impairments after sepsis is unknown. However, even patients with normal neurocognitive testing after sepsis may report new difficulties with memory and executive functioning that limit return to work or school.<sup>43</sup>

### Mental Health Impairment

Patients discharged from an ICU report a high prevalence of anxiety (32%) within 2 to 3 months<sup>44</sup>; depression (29% within 2 to 3 months)<sup>45</sup>; and posttraumatic stress disorder (PTSD) symptoms (44%) within 1 to 6 months<sup>46</sup> (eTable in the Supplement). Among 2 studies of patients after sepsis, rates of mental health impairments were high.<sup>47,48</sup> Sepsis was an independent risk factor of stress disorders after critical illness in observational studies.<sup>48,49</sup> Somatic symptoms of depression, such as weakness, appetite change, and fatigue, were common.<sup>50</sup>

The extent to which anxiety, depression, or PTSD are exacerbated by sepsis is unclear. In a study involving 439 Health and Retirement Study participants, the prevalence of clinically significant depressive symptoms was 28% before sepsis and 28% after sepsis. However, in a population-based Danish cohort, 9912 critically ill patients without prior psychological history were more likely than hospitalized controls to receive new psychoactive prescriptions (12.7% vs 5.0%; adjusted HR, 2.5; 95% CI, 2.19–2.74;  $P < .001$ ) or new psychiatric diagnoses (0.5% vs 0.2%; adjusted HR, 3.4; 95% CI, 1.96–5.99;  $P < .001$ ) in the 3 months after hospitalization.<sup>51</sup> It is unclear whether depression, anxiety, or PTSD are exacerbated by sepsis, or merely more common among patients who develop sepsis. However, it is important to recognize and treat mental health impairments because they are associated with a more complicated clinical course.<sup>52,53</sup>

### Recurrent Infection and Sepsis

Patients are susceptible to health deterioration after sepsis recovery (Table 1). In a study involving 2617 Medicare beneficiaries who survived hospitalization for sepsis, 40% were readmitted within 90 days.<sup>37</sup> The most common readmission diagnosis was infection; 11.9% were readmitted for sepsis, pneumonia, urinary tract, or skin or soft tissue infection compared with 8.0% of age- and comorbidity-matched patients surviving hospitalizations for other acute medical diagnoses ( $P < .001$ ).<sup>37</sup> In a nationwide study involving 10 818 patients who survived hospitalization for sepsis in Taiwan, risk of subsequent sepsis was elevated 9-fold (from 4.3% to 35.0%) relative to matched population controls.<sup>39</sup>

### Exacerbation of Chronic Medical Conditions

Patients discharged after treatment for sepsis have high rates of hospital readmission for conditions that are potentially treatable in the outpatient setting, including exacerbation of congestive heart failure, acute renal failure, and exacerbation of chronic obstructive pulmonary disease<sup>37</sup> (Table 1). These diagnoses reflect common comorbidities of patients

who develop sepsis and conditions that may be exacerbated by sepsis-induced organ dysfunction (eg, reduced glomerular filtration rate) or impaired homeostatic mechanisms (eg, labile blood pressure or fluid imbalance).

Risk of cardiovascular events and acute renal failure are increased relative to matched controls, suggesting that sepsis may directly contribute to the development or progression of these conditions. In 2 observational studies involving 4179 and 67 926 patients who survived hospitalization for sepsis, the incidence of new cardiovascular events (myocardial infarction, stroke, sudden cardiac death, and ventricular arrhythmias) was increased 1.4- to 1.9-fold relative to population controls, and 1.1- to 1.3-fold relative to hospitalized controls.<sup>8,38</sup> Among 2617 Medicare beneficiaries discharged after sepsis, risk of 90-day readmission for acute renal failure was increased 2.7-fold for patients with sepsis (3.3%) vs matched patients (1.2%;  $P < .001$ ).

### **Other Symptoms and Sequelae**

Patients may report other symptoms, such as numbness, pain, visual disturbance, hair loss, and problems with dentition and nails.<sup>54</sup> Amputation due to limb gangrene is a rare but extreme sequela of sepsis, which may occur from cardiovascular shock, microcirculatory dysfunction, or high vasopressor dosages.<sup>55</sup>

### **Impact on Quality of Life, Return to Work, and Social Relationships**

Patients who survive sepsis report lower quality of life compared with population averages and often cannot resume prior roles or activities.<sup>56</sup> For example, in one study, 35% of elderly patients were discharged to a postacute care facility.<sup>12</sup> Only 43% of previously employed patients returned to work within a year of contracting septic shock,<sup>57</sup> and only 33% of patients living at home prior to contracting sepsis returned to independent living by 6 months after discharge.<sup>58</sup> Spouses and family members must often serve as informal caregivers. A study<sup>47</sup> of spouses caring for partners who had survived sepsis found that the spouses were at increased risk of depression with 20% having depressive symptoms before sepsis vs 34% after sepsis.

### **Hospital and ICU-Based Strategies to Prevent Adverse Sequelae After Sepsis**

Current treatment guidelines emphasize interventions that reduce short-term mortality, with little information on strategies to minimize physical disability, cognitive impairment, or health deterioration after sepsis. It is uncertain whether improvement in 30-day outcomes are associated with lasting benefit; there may be instances when that is not the case. For example, conservative fluid administration during sepsis-induced acute respiratory distress syndrome was shown to reduce ICU length of stay and increase ventilator-free days but was subsequently associated with worse late cognitive function, possibly due to compromised cerebral perfusion.<sup>59</sup> Although data are limited, Our strategy for preventing long-term sequelae after sepsis focuses on 3 strategies: high-quality early sepsis care<sup>10</sup>; management of pain, agitation, and delirium<sup>60</sup>; and early mobilization to prevent or minimize muscle atrophy<sup>60</sup> (Table 2).

## Early Hospital Treatment for Sepsis

Early hospital care for sepsis focuses on prompt recognition, treatment with broad-spectrum antibiotics, elimination of infectious sources (eg, removing infected indwelling catheters), and resuscitation with intravenous fluids and vasopressors for patients with low blood pressure or elevated lactate.<sup>10</sup> In a recent observational study involving 49 331 patients, prompt delivery of these treatments was associated with improved survival (odds ratio for in-hospital mortality, 1.04 per hour delay to antibiotic administration,  $P < .001$ ).<sup>63</sup> Earlier treatment may also result in fewer long-term sequelae by minimizing duration of pathogen invasion, host response, host-pathogen interaction, and limiting the opportunity for adverse sequelae.

## Pain, Agitation, and Delirium Management During Hospitalization for Sepsis

In critically ill patients, pain, agitation, and delirium are common complications that are associated with increased risk of mortality, cognitive impairment, and PTSD.<sup>64</sup> Clinical practice guidelines recommend (1) completing regular assessments of pain using a validated scale (eg, Behavioral Pain Scale or Critical Care Pain Observation Tool); (2) prescribing intravenous narcotic analgesics as the first-line pharmacological treatment for pain; (3) using short-acting sedative medications (eg, propofol or dexmedetomidine) over benzodiazepines; (4) monitoring depth of sedation using a validated scale (eg, Richmond Agitation Sedation Scale or Sedation Analgesia Scale); (5) maintaining light levels of sedation (ie, a patient should be arousable and able to respond to simple commands); (6) stopping continuous sedative medications at least once daily to allow patients to awaken and be reoriented; and (7) monitoring for delirium regularly using a validated scale (eg, Confusion Assessment Method for the ICU or Intensive Care Delirium Checklist). Lighter sedation is associated with lower 1-year mortality (eg, 44% in patients randomized to less sedation combined with a ventilation weaning protocol vs 58% with usual care,  $P = .01$ ),<sup>65</sup> without increased risk of PTSD.<sup>66</sup>

## Early Mobility

In a randomized clinical trial (RCT),<sup>67</sup> early mobilization, which promotes early and progressive activity (bed-based exercises, to sitting, standing, and ultimately walking), resulted in shorter time to physical therapy (median, 1.5 vs 7.4 days;  $P < .001$ ), time to ambulation (median, 3.8 vs 7.6 days;  $P < .001$ ), and duration of delirium (median 2.0 vs 4.0 days,  $P = .03$ ) during hospitalization. Randomization to early mobility interventions has also been associated with improved physical function at hospital discharge<sup>67–69</sup> and increased likelihood of being discharged directly home (53 of 104 [51%] vs 26 of 96 [27%],  $P < .001$ ).<sup>68</sup> Although early mobility has not been proven to improve late physical function, it is possible that short-term improvement in function also results in improvement in long-term (eg, 6-month) function.

## Postdischarge Assessment and Treatment of Sepsis Survivors

There is limited clinical trial evidence to guide management of patients after hospitalization for sepsis<sup>70,71</sup> (Table 3). Randomized clinical trials to promote recovery after critical illness have examined specialized nurse-led ICU follow-up clinics,<sup>79,80</sup> in-person exercise

rehabilitation programs,<sup>73–75</sup> provision of self-guided exercise rehabilitation manuals,<sup>72</sup> and case management interventions.<sup>76,77</sup> However, these interventions have yielded only small and inconsistent benefits in short- and moderate-term physical function by patient report (eg, 36-Item Short Form Physical Function Component) or physical assessment (eg, anaerobic threshold).

The only RCT<sup>78</sup> that studied recovery after sepsis hospitalization randomized 291 patients to a multicomponent primary care management intervention vs usual care. The intervention included education for patients and clinicians about sepsis and its common sequelae; case management by nurses with ICU experience, focusing on proactive symptom monitoring; and decision support by physicians trained in both primary and critical care. The primary outcome was mental health—related quality of life at 6 months. However, 32 outcomes were measured, each at 6 and 12 months. The intervention group performed better on 5 of 64 outcomes (Short Musculoskeletal Function Assessment, Physical Function (XSMF-A [Extra Short Musculoskeletal Function Assessment regarding physical function] ) and Disability (XSMF-B) scales at 6 months, ADL limitations at 6 and 12 months, and Regensburg Insomnia Scale at 12 months), suggesting a potential effect on functional outcomes.<sup>78</sup> However, given the number of outcomes measured, these positive findings must be considered exploratory.<sup>78</sup>

Despite the lack of high-quality evidence, several expert panels suggest that rehabilitation with physical, occupational, and speech therapy benefits patients who develop new weakness following sepsis.<sup>69,81</sup> The National Institute for Health and Care Excellence's Guidelines on Rehabilitation after Critical Illness recommend multiprofessional rehabilitation after critical illness,<sup>62</sup> starting in the ICU and continuing in the ward and after hospital discharge. Indirect evidence also comes from the benefits of physical rehabilitation in related populations, such as older patients with cognitive impairment,<sup>82</sup> patients surviving stroke or traumatic brain injury,<sup>83,84</sup> and residents in long-term care.<sup>85</sup> In addition, an observational study of 30 000 sepsis survivors showed that referral to rehabilitation within 90 days of hospital discharge was associated with lower risk of 10-year mortality compared with propensity-matched controls (adjusted HR, 0.94; 95% CI, 0.92–0.97;  $P < .001$ ).<sup>86</sup> Furthermore, a small pilot RCT<sup>74</sup> of a multicomponent post-ICU rehabilitation program incorporating cognitive, functional, and physical rehabilitation showed improved cognitive and functional outcomes at 3 months using the Tower test for planning and strategic thinking (median, 13.0; interquartile range, 11.5–14.0 vs 7.5; interquartile range, 4.0–8.5; adjusted  $P < .01$ ), suggesting that neurocognitive deficits may be also be amenable to treatment.

Patients with new impairments that are not rapidly improving should be referred for assessment by a physical, occupational, or speech therapist, given the strong theoretical rationale for benefit. The goals of rehabilitation, as in analogous clinical situations, include improving exercise capacity, strengthening skeletal and respiratory muscles, and promoting independent completion of ADLs.<sup>81</sup> Potential tools to screen for new functional disability warranting referral include the Katz Index of ADLs, Timed Up and Go test, and 6-minute walk distance.



## Screening for Treatable Medical Conditions

Physicians should assess patients' risk of common and potentially preventable causes of hospital readmission (infection, congestive heart failure exacerbation, acute renal failure, chronic obstructive pulmonary disease exacerbation, and aspiration pneumonitis) and tailor medical care to anticipate and prevent these problems (Box).

### Box

#### Framework for Evaluating and Treating Patients in the 90 Days After Hospitalization for Sepsis<sup>a</sup>

##### Screen for Common, Treatable Impairments After Sepsis

##### Functional Disability

Patients aged 65 years or older develop an average of 1 to 2 new functional limitations<sup>6</sup>

For patients with newly reduced exercise capacity, consider enrollment in a clinical trial of rehabilitation. If a trial is not available, consider referral to physical therapy, referral to pulmonary or cardiac rehabilitation, or prescribe a structured exercise program, depending on the severity of impairments and motivation of the patients

For patients with new limitations of activities or instrumental activities of daily living, consider referral to occupational therapy

If sepsis has occurred in the setting of long-standing comorbidity and declining health, discuss whether transition to palliative focus is appropriate

##### Swallowing Impairment

Of patients aged 65 years or older, 1.8% (95% CI, 1.3%–2.3%) are readmitted within 90 days for principal diagnosis of aspiration pneumonitis<sup>37</sup>

For patients with evidence of swallowing impairment (dysphagia, weak voice, or cough), consider referral to speech therapy for further evaluation (eg, fluoroscopic swallow evaluation) and treatment (eg, swallow strengthening exercises, modified diet)

##### Mental Health Impairments

Point prevalence for clinically significant anxiety is 32% (95% CI, 27%–38%) at 2 to 3 months<sup>41</sup>; for depression, 29% (range, 22%–36%) at 2 to 3 months<sup>42</sup>; and for PTSD, 44% (range, 36%–52%) at 1 to 6 months<sup>43</sup>

Review the details of the hospital course with interested patients because ICU diaries are associated with decreased PTSD

Consider screening for depression and anxiety with validated surveys

Consider referring patients and caregivers to peer support programs or mental health services

##### Review and Adjust Long-term Medications

## Medication Errors

Errors of omission occur in 10% to 25% of patients, depending on medication class.<sup>25</sup>  
Errors of commission occur in 1% to 25%, depending on medication class<sup>26,27</sup>

Confirm that long-term medications should remain on list

Discontinue hospital medications without ongoing indication (eg, inhalers, atypical antipsychotics, gastric acid suppressants)

Assess whether any doses should be adjusted based on changes in body mass, renal, or cardiac function, focusing on diuretics, antihypertensives, and renally cleared medications

## Anticipate and Mitigate Risk for Common and Preventable Causes of Health Deterioration

### Infection

Of patients aged 65 years or older, 11.9% (95% CI, 10.6%–13.1%) are readmitted within 90 days for principal diagnosis of infection (sepsis, pneumonia, urinary tract, and skin or soft tissue infection), 6.4% are readmitted for a principal diagnosis of sepsis<sup>37</sup>

Counsel patients about their risk of infection and recurrent sepsis

Ensure receipt of vaccines appropriate for the patient

Encourage patients to seek medical care for infectious signs and symptoms

Counsel patients on signs and symptoms that infection has progressed to sepsis (eg, decreased urine output, confusion, cyanosis, mottled skin), indicating that immediate evaluation is needed

For patients presenting with signs or symptoms of infection, consider chest x-ray, complete blood cell count, urinalysis, or cultures to confirm or rule out suspected infection

Schedule in-person or telephone follow-up to monitor for symptomatic improvement in patients with suspected infection

### Heart Failure Exacerbation

Of patients aged 65 years or older, 5.5% (95% CI, 4.6%–6.4%) are readmitted within 90 days for principal diagnosis of congestive heart failure<sup>37</sup>

Reassess need and dosage for diuretics,  $\beta$ -blockers, and ACE-inhibitors because dosage requirements may change after sepsis due to changes in body weight, renal function, or cardiac function

Monitor volume status and weight at each visit, recognizing that dry weight may have declined due to lost muscle mass

### Acute Renal Failure

Of patients aged 65 years or older, 3.3% (range, 2.6%–4.0%) were readmitted within 90 days for principal diagnosis of acute renal failure<sup>37</sup>

For patients with acute renal injury during sepsis, consider surveillance laboratory testing to ensure that renal function improves or stabilizes (eg, check chemistry panel once a week for 3 weeks, then monitor less frequently once blood work is stable)

Reassess need and dosages for renally cleared and nephrotoxic agents (eg, ACE-inhibitors, NSAIDs, statins, ranitidine, opiates, benzodiazepines)

### **COPD Exacerbation**

Of patients aged 65 years or older, 1.9% (95% CI, 1.4%–2.4%) are readmitted within 90 days for principal diagnosis of COPD exacerbation<sup>37</sup>

Confirm and initiate appropriate controller inhalers

Ensure receipt of vaccines appropriate for the patient

Review and consider stopping or reducing dosages of medications that may suppress respiration such as benzodiazepines and opiates

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PTSD, posttraumatic stress disorder.

<sup>a</sup> This Box provides a framework to approach medical evaluation and treatment of patients who have recently survived sepsis hospitalization. Posthospital care should focus on screening for new impairments; reviewing and adjusting long-term medications; and screening for common, preventable causes for medical deterioration.

### **Medications**

Physicians should review a patient's medication list at hospital discharge, resume essential medications that may have been held during the hospital stay, and assess whether any newly added medications can be discontinued. Patients' glomerular filtration rate, fluid balance, vascular tone, and weight may be labile in the weeks following hospitalization. Doses of antihypertensives, diuretics, and renally cleared medications should be reassessed at each visit until patients have stabilized.

### **Referrals**

Because of the heterogeneity of potential problems after sepsis, clinicians may consider early referrals to multiple subspecialists and ancillary services. However, it is important to consider the experience of sepsis survivors within the cumulative complexity model framework,<sup>87</sup> which conceptualizes patient experience as a balance between workload (the work of being a patient, including effort to understand, access, and use medical care) and capacity (the quality and availability of resources to facilitate being a patient). This framework acknowledges the challenges of adhering to medical care, and suggests that overly complex treatment plans have limitations. Patients with a recent sepsis hospitalization may experience several new barriers to carrying out treatment plans, such as new weakness, cognitive impairment, fatigue, lost income, or stressed caregivers. Clinicians should be

aware of these challenges and should consider starting with 1 or 2 referrals to address the most significant symptoms, then place additional referrals over time.

### **Self-management**

Patients and caregivers should be educated about sepsis (including common sequelae) and informed of peer support resources. Many patients are unaware of their sepsis diagnosis,<sup>88</sup> and even fewer realize its association with long-term disability.<sup>89</sup> Intensive care unit diaries—nonmedical accounts of a patient’s hospitalization written by nurses and family members—are shown to reduce PTSD symptoms when provided to patients and caregivers 1 month after an ICU stay.<sup>90,91</sup> Although ICU diaries are uncommon outside Europe, providing a narrative of the hospital course in understandable terms to interested patients may provide similar benefit. Peer-to-peer support groups, a common resource for patients with cancer and other chronic diseases, have not existed for patients suffering the sequelae of sepsis until recently.<sup>92</sup> Since 2015, Society of Critical Care Medicine has organized a growing number of in-person, online, and telephone-based support groups for patients and families surviving critical illness.<sup>92</sup> Patients and families may benefit from sharing their story, receiving empathy, and learning coping mechanisms from others who have overcome or adapted to new impairments.<sup>92</sup>

### **Establishing Goals of Care**

Given the high rates of death,<sup>13</sup> disability,<sup>6</sup> and health care use after sepsis, it is important to discuss goals of care and consider whether a palliative focus is appropriate, in particular for patients with declining health prior to sepsis. However, despite reduced quality of life relative to population norms,<sup>56</sup> long-term sepsis survivors are often satisfied with their quality of life and would undergo ICU treatment again.<sup>93</sup> Patient-specific conversation is needed.

### **Important Unanswered Questions**

Many important questions about postsepsis morbidity remain unanswered. Researchers generally consider sepsis from the starting point of hospital admission. Although this may be appropriate for healthy patients, it may be inappropriate for patients whose health was declining prior to sepsis. Future research is needed to better characterize how presepsis health affects long-term outcomes after sepsis.

### **Is Sepsis Different From Any Other Hospitalization?**

Many challenges described above apply to all patients surviving acute illness.<sup>24,25</sup> However, certain sequelae (eg, immunosuppression) may be more common after sepsis, while other aspects of care (eg, confirming correct medications) may be particularly important to address after sepsis.

### **Which Aspects of Illness and Treatment Contribute to Which Postsepsis Sequelae?**

Long-term sequelae may be associated with both disease (eg, infection, organ dysfunction) and treatment (eg, sedation). Measuring the individual contributions of characteristics of

sepsis and sepsis treatment to outcomes is challenging but necessary for targeting interventions to the most important mediators of long-term adverse sequelae.

### Can Adverse Sequelae Be Prevented?

The most common outcome in RCTs of sepsis is mortality. Interventions that reduce mortality are assumed to be uniformly beneficial. However, interventions that reduce short-term mortality may increase long-term mortality or worsen other patient-centered outcomes such as physical disability.<sup>94</sup> As survival from sepsis improves, the effect of interventions on long-term physical and cognitive function must be explicitly tested.

### Which Clinicians Should Address Postsepsis Morbidity?

With increasing specialization of medical care, it is unclear who is best suited to address postsepsis morbidity and in what setting. Multi-disciplinary clinics for post-ICU care have been established in several countries,<sup>95</sup> but their benefit is unknown. A multicenter collaborative was recently established to study and refine best practices for post-ICU clinics.<sup>96</sup>

## Conclusions

As in-hospital sepsis mortality has decreased, an estimated 14 million patients survived hospitalization for sepsis in 2016. These patients often acquire new physical disability and cognitive impairment following sepsis and may experience further health deterioration after hospital discharge. Risk of subsequent infection, cardiovascular events, acute renal failure, and aspiration are increased after hospitalization for sepsis. Further research is needed to determine the optimal approach to caring for patients who have survived sepsis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding/Support:** This work was supported by grants K08 GM115859 (Dr Prescott) and R01 GM097471 (Dr Angus) from the National Institute of General Medical Sciences of the National Institutes of Health.

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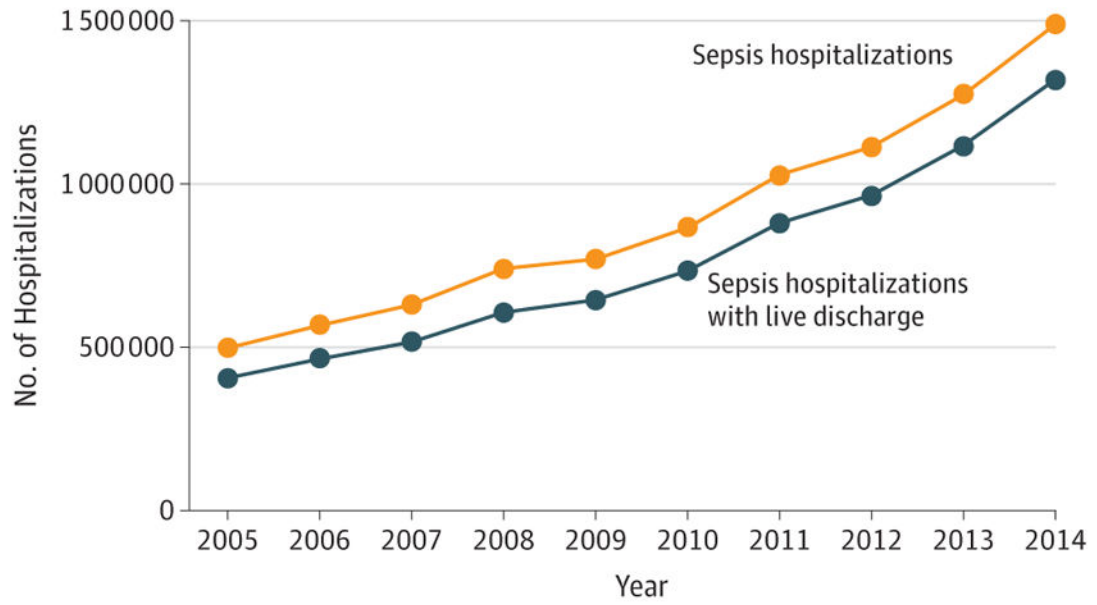
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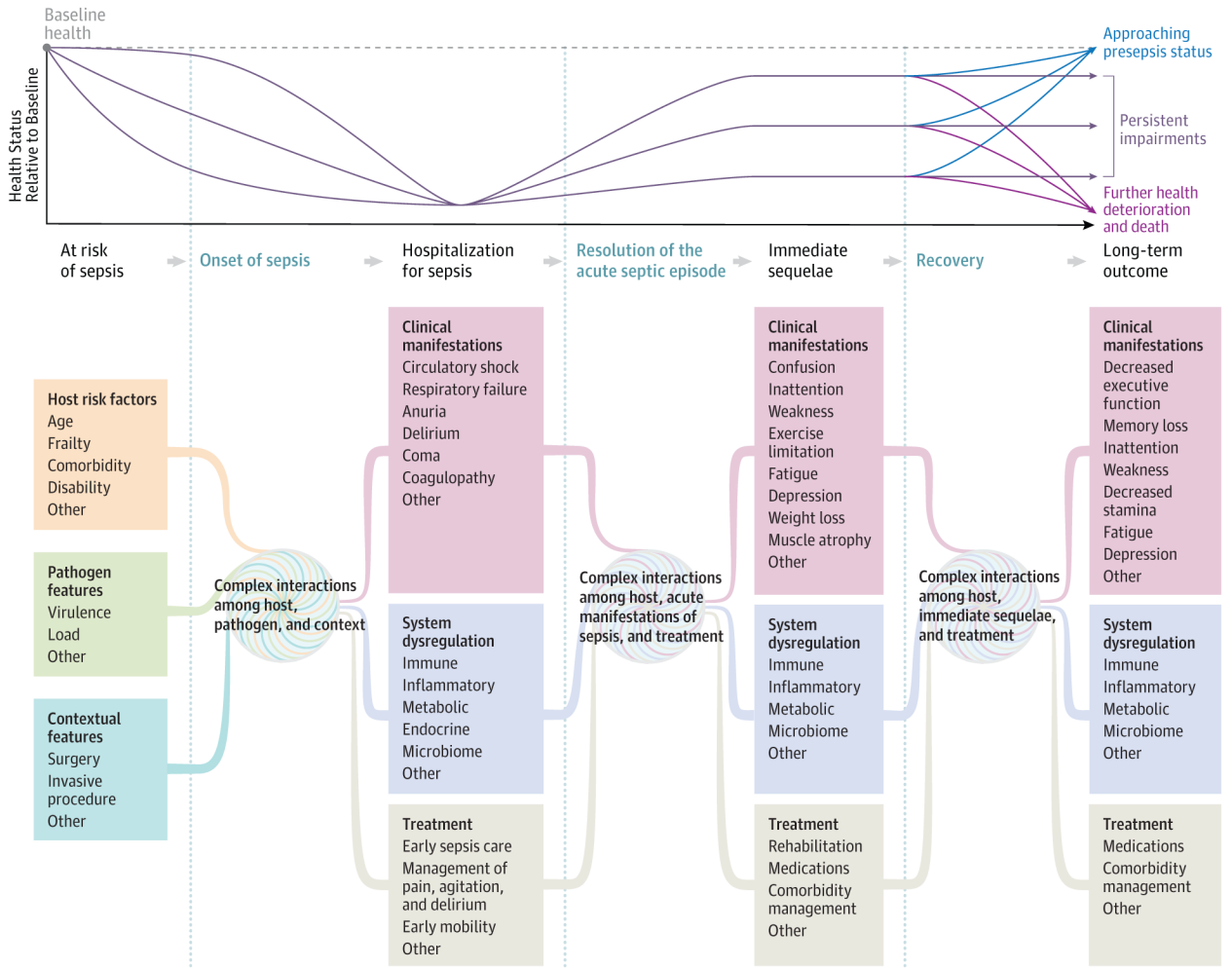


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**Figure 1. US Hospitalizations and Live Discharges for a Diagnosis of Sepsis, 2005–2014**  
 This figure depicts the number of adult hospitalizations and live discharges in the United States with a principal diagnosis of sepsis, severe sepsis, or septic shock over time. The data were abstracted from the National Inpatient Sample using HCUPnet.<sup>11</sup>



**Figure 2. A Conceptual Model of the Potential Network of Factors and Interactions Important to Determining a Patient’s Clinical Course and Long-term Outcome After Sepsis**  
 There are many potential clinical courses that a patient may experience after a hospitalization for sepsis, from rapid complete recovery to recurrent complications and death. This figure depicts examples of common clinical trajectories and presents a conceptual model of factors important to shaping a patient’s clinical course and long-term outcome. This figure draws from the Wilson-Cleary model,<sup>18</sup> which links underlying biological factors to physical function and quality of life, but extends the representation of the biological factors to demonstrate their complex and unmeasurable interactions.

**Table 1**

**Matched Cohort Studies Examining Risk for Physical Disability, Cognitive Impairment, and Common Medical Conditions in Patients Surviving a Hospitalization for Sepsis<sup>a</sup>**

Source	Study Population	Comparison	Findings
<b>Physical Disability</b>			
Iwashyna et al, <sup>6</sup> 2010	516 HRS participants who survived hospitalization for sepsis, 65 y with linked Medicare claims	4517 HRS participants, 65 y, who survived a nonsepsis hospitalization	Patients with no functional limitations prior to sepsis developed a mean 1.57 new limitations (95% CI, 0.99–2.15) after sepsis vs 0.48 new limitations among comparison patients (P < .001 for difference) Patients with mild to moderate limitations before sepsis developed a mean 1.50 new limitations (95% CI, 0.87–2.12) after sepsis hospitalization; 59.3% (95% CI, 55.5%–63.2%) of patients who completed follow-up assessment (median, 1 y postsepsis) had worse cognitive or physical function than their own presepsis baseline assessment
<b>Cognitive Impairment</b>			
Iwashyna et al, <sup>6</sup> 2010	516 HRS participants who survived hospitalization for sepsis, 65 y, with linked Medicare claims	4517 HRS participants, 65 y, who survived a nonsepsis hospitalization	Moderate to severe cognitive impairment increased 10.6% after sepsis, from 6.1% presepsis to 16.7% postsepsis In a multivariable model, sepsis was associated with an adjusted OR of 3.34 (95% CI, 1.53–7.25) for developing moderate to severe cognitive impairment (P < .001), while nonsepsis hospitalization was not associated with increased odds (adjusted OR, 1.15; 95% CI, 0.80–1.67)
Shah et al, <sup>7</sup> 2013	198 CHS participants who survived a hospitalization for sepsis, 320 pneumonia, or 1049 infection	2556 CHS participants not hospitalized with infection	Adjusted HRs for progression to dementia were 2.28 (95% CI, 1.38–3.77) postsepsis, 2.24 (95% CI, 1.62–3.11) after pneumonia, and 1.98 (95% CI, 1.61–2.43) after infection (P < .001 for each)
<b>Common Medical Conditions</b>			
Yende et al, <sup>8</sup> 2014	4179 Medicare beneficiaries who survived an ICU hospitalization for sepsis	4179 Medicare beneficiaries hospitalized in ICU without sepsis; 4179 hospitalized with infection; 4179 hospitalized without infection, and 4179 nonhospitalized. All controls were matched on age, sex, prior cardiovascular disease, and propensity for sepsis	Cardiovascular events occurred 29.5% of patients in the year after sepsis (498.2 events/1000 person-y) Rate of cardiovascular events was higher after sepsis vs matched population controls (incidence RR, 1.9; P < .01) and matched hospitalized controls (incidence RR, 1.1; P = .002). Rates were indistinguishable from matched ICU controls (P = .28)
Zielske et al, <sup>36</sup> 2014	30 Adult survivors of ICU stay with sepsis	30 Adult survivors of ICU stay without sepsis	After 14 d in the ICU, aspiration was present on fiberoptic endoscopic evaluation of swallowing in 63% (19/30) of patients with sepsis vs 23% (7/30) of patients without sepsis (P = .002)
Prescott et al, <sup>37</sup> 2015	2617 HRS participants who survived a sepsis hospitalization, 65 y with linked Medicare claims	2617 Age, sex, and health status–matched HRS participants who survived a hospitalization for a nonsepsis acute medical condition	90-d Hospital readmission for a principal diagnosis of infection occurred in 11.9% (95% CI, 11.9%–13.1%) after vs in 8.0% (95% CI, 7.0%–9.1%) of controls (P < .001) P Readmission for sepsis occurred in 167 patients (6.4%) of 2617 vs 73 (2.8%; P < .001) Readmission for acute renal failure occurred in 87 (3.3%) vs 30 (1.2%; P < .001) Readmission for acute respiratory failure occurred in 65 (2.5%) vs 38 (1.5%; P = .007) Readmission for aspiration pneumonitis occurred in 47 (1.8%) vs 31 (1.2%; P = .06)
Ou et al, <sup>38</sup> 2016	All 93 862 adult patients hospitalized with sepsis in Taiwan during a 3-y period, of whom, 67 926 were matched to population controls and 42 855 were matched to nonsepsis hospitalizations	67 926 Population controls and 42 855 survivors of nonsepsis hospitalization, matched by propensity for sepsis hospitalization	During long-term follow-up (average 6.7 y), patients postsepsis had increased risk of cardiovascular events vs matched population controls (adjusted HR, 1.37; 95% CI, 1.34–1.41) and matched survivors on nonsepsis hospitalization (adjusted HR, 1.27; 95% CI, 1.22–1.32)

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Source	Study Population	Comparison	Findings
Shen, et al, <sup>39</sup> 2016	All 10 818 adult patients hospitalized with sepsis in Taiwan during a 3-y period, who had no prior sepsis and survived to 90 d without recurrent sepsis	10 818 Age- and sex-matched population controls with no prior history of sepsis	During 8-y follow-up, 35.0% of patients after sepsis vs 4.3% of matched controls had a recurrent hospitalization for sepsis Adjusted HR for subsequent sepsis among sepsis survivors, 8.89 (95% CI, 8.04–9.83)

Abbreviations: CHS, Cardiovascular Health Study, an observational cohort study; HR, hazard ratio; HRS, US Health and Retirement Study, an observational cohort study; ICU, intensive care unit; OR, odds ratio; RR, rate ratio.

<sup>a</sup>Ou et al<sup>38</sup> defined sepsis by principal diagnosis of sepsis (*ICD-9-CM*038.x). All other studies identified sepsis by evidence of acute infection plus acute organ dysfunction.

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**Table 2**

Recommended Practices for Reducing Long-term Morbidity in Septic and Critically Ill Patients

Element of Care	Guideline Recommendation	Guideline	Level of Evidence <sup>d</sup>
<b>Early Sepsis Care</b>			
Antibiotics	Recommendation: empirical broad-spectrum therapy with 1 antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens	SSC	Moderate
	Administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock	SSC	Moderate
Fluid resuscitation	In the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid should be given within the first 3 h	SSC	Low
Vasopressors	Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure ≥ 65 mm Hg within the first 6 h	SSC	Low
Source control	A specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible. Any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made	SSC	Ungraded
	Recommendation: prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established	SCC	Ungraded
<b>Pain, Agitation, and Delirium Management</b>			
Pain assessment	Pain should be routinely monitored for adult ICU patients using validated scales such as Behavioral Pain Scale or Critical-Care Pain Observation Tool	PAD	Moderate
Pain treatment	Intravenous opioids should be considered the first-line drug class of choice to treat nonneuropathic pain in critically ill patients	PAD	Low
Sedative choice	Recommendation: analgesia-first sedation for mechanically ventilated adult ICU patients	PAD	Moderate
	Sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients	PAD	Moderate
Sedative monitoring	Richmond Agitation-Sedation Scale and Sedation-Agitation Scale are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients	PAD	Moderate
Depth of sedation	Sedative medications should be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated	PAD	Moderate
	Recommendation: either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients	PAD	Moderate
	Recommendation: that continuous or intermittent sedation be minimized for mechanically ventilated sepsis patients, targeting specific titration end points	SSC	Ungraded
Delirium monitoring	Recommendation: routine monitoring of delirium in adult ICU patients	PAD	Moderate
	The Confusion Assessment Method for the ICU and the Intensive Care Delirium Screening Checklist are the most valid and reliable delirium-monitoring tools in adult ICU patients	PAD	High
<b>Early Mobility</b>			
Mobilization	Recommendation: performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium	PAD	Moderate
	During the patient's critical care stay and as early as clinically possible, perform a short clinical assessment to determine the patient's risk of developing physical and nonphysical morbidity.	NICE	Ungraded
	For patients at risk of physical and nonphysical morbidity, perform a comprehensive clinical assessment to identify their current rehabilitation needs.	NICE	Ungraded

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Element of Care	Guideline Recommendation	Guideline	Level of Evidence <sup>a</sup>
	This should include assessments by health care professionals experienced in critical care and rehabilitation.		
	For patients at risk, start rehabilitation as early as clinically possible, based on the comprehensive clinical assessment and the rehabilitation goals.	NICE	Ungraded

Abbreviations: ICU, intensive care unit; PAD, clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit<sup>61</sup>; NICE, National Institute for Health Care and Excellence Clinical Guideline on Rehabilitation after Critical Illness<sup>62</sup>; SSC, Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock: 2016.<sup>10</sup>

<sup>a</sup>For SSC and PAD, level of evidence is graded as high (high-quality randomized clinical trial [RCT]), moderate (downgraded RCTs or upgraded observational studies), or low (observational study).

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**Table 3**  
Randomized Clinical Trials of Postdischarge Rehabilitation Interventions for Survivors of an Intensive Care Unit Stay

Source		Location	No.	Characteristics	No. (%) With Sepsis	Mean Age, y	Intervention	Control	Trial Length	Primary Outcomes
<b>Rehabilitation Programs</b>										
Jones et al, <sup>72</sup> 2003	United Kingdom	126	Adult ICU survivors who received mechanical ventilation	Not reported	58	Routine ICU follow-up, plus a 6-wk self-help rehabilitation manual	Routine ICU follow-up, consisting of 2 general ward visits, 3 telephone calls at home, and follow-up in a dedicated ICU follow-up clinic at 8 wk and 6 mo	6 mo	"A repeated-measures ANOVA (group by time interaction effect) of the SF-36 physical function scores at the 3 time points (premorbid, 8 wk, and 6 mo), when controlled for length of ICU stay, was significant, $P=.006$ ." Anxiety (HADS-A) was present in 33% (19/58) of intervention vs 34% (15/44) of control patients at 6 mo ( $P>.05$ ) Depression (HADS-D) was present in 12% (8/63) of intervention vs 25% (13/51) of control patients at 8 wk ( $P=.07$ ) and 10% vs 12% at 6 mo ( $P>.05$ ) IES scores were "lower in the intervention patients at 8 wk" (absolute numbers not reported; $P=.03$ ) PTSD (IES>19) was present in 53% (31/58) vs 48% (21/44) at 6 mo ( $P=.57$ )	
Elliot, et al, <sup>73</sup> 2011	Australia and New Zealand	195	Adult ICU survivors who received mechanical ventilation 24 h, mean APACHE II score, 19; median ICU LOS, 6 d	Not reported (8)	57	8-wk Individualized home-based physical rehabilitation program, including 3 physical trainer home visits, 4 follow-up telephone calls, and a printed exercise manual	Community-based care (eg, visits to primary care physician). 3 visits for study assessment only	6 mo	Estimated treatment effects (change in intervention minus change in control patients) at 8 wk were 0.7 (95% CI, -2.5 to 3.8) for SF-36 physical function subscale, 8.4 m (95% CI, -29.6 to 46.4 m) for 6-minute walk distance, -1.3 (95% CI, -4.3 to 1.7) for SF-36 Physical Component Summary, and 1.8 (95% CI, -2.6 to 6.2) for SF-36 Mental Component Summary. Differences at 26 wk were 0.9 (95% CI, -2.7 to 4.6) for SF-36 physical function subscale, 9.6 m (95% CI, -31.4 to 50.5 m) for 6-minute walk distance, 0.3 (95% CI, -3.2 to 3.7) for SF-36 Physical Component Summary, and 1.5 (95% CI, -3.1 to 6.2) for SF-36 Mental Component Summary	
Jackson et al, 74 2012	United States	21	Adult survivors of an ICU	6 (30.0)	47	12-wk Home-based cognitive, physical,	Usual care: referral to	3 mo	At 3 mo, median Tower score (overall executive functioning), 13.0 (IQR,	

Patients									
Source	Location	No.	Characteristics	No. (%) With Sepsis	Mean Age, y	Intervention	Control	Trial Length	Primary Outcomes
Batterham et al, <sup>75</sup> 2014	United Kingdom	59	Adult ICU survivors who received mechanical ventilation 72 h, mean APACHE II score, 16; median ICU LOS, 15 d	31 (52.5)	42	8-wk Physiotherapist-supervised exercise program, consisting of 2 physiotherapist-led ergometer exercise sessions plus 1 unsupervised exercise session per wk	Usual care	6 mo	9-wk Difference in anaerobic threshold (in mL O <sub>2</sub> kg <sup>-1</sup> min <sup>-1</sup> ), 1.8 (95% CI, 0.4 to 3.2); difference in SF-36 Physical Function sub-scale, 3.4 (95% CI, -1.4 to 8.2); and difference in SF-36 Mental Health sub-scale, 1.9 (95% CI, -3.9 to 7.7); 26-wk difference in anaerobic threshold, 0.6 (95% CI, -1.6 to 2.8); difference in SF-36 Physical Function subscale, 0.1 (95% CI, -6.0 to 6.2); and difference in SF-36 Mental Health subscale, 4.4 (95% CI, -2.4 to 11.2); differences in secondary outcomes (EQ-5D, HADS-A, HADS-D) were not significant at either time point
<b>Case Management and/or Enhanced Primary Care</b>									
Daly et al, <sup>76</sup> 2005 Douglas et al, <sup>77</sup> 2007	United States	334	Adult ICU survivors who received mechanical ventilation for at least 72 h, mean APACHE III, 76; mean ICU LOS, 16 d	Not reported; but 399 (38.3) had pneumonia	62	2-mo Disease management program, including care coordination, family support, education, and monitoring of treatment by advanced-practice nurse with geriatrician and pulmonologist consultation	Usual care	2 mo	Hospital readmission occurred in 40.4% (93/231) of intervention vs 41.9% (39/103) of control patients, P = .65. Mean time to readmission was 15.9 d (95% CI, 12.8–18.9 d) vs 13.9 d (95% CI, 9.4–18.5 d; P = .64); mean No. of days spent readmitted was 11.4 (95% CI, 9.3–12.6) vs 16.7 (95% CI, 12.5–21.0; P = .03)
Schmidt et al, <sup>78</sup> 2016	Germany	291	Adult survivors of an ICU hospitalization for	291 (100)	61	12-mo Primary Care Management Program, including	Usual care	1 y	Estimated treatment effect (change in intervention minus change in control patients) for primary outcome SF-36

Patients		No.	Characteristics	No. (%) With Sepsis	Mean Age, y	Intervention	Control	Trial Length	Primary Outcomes
			severe sepsis or septic shock, 84% received mechanical ventilation, mean ICU LOS, 34 d			patient and clinician education, case management, and consultant decision support			Mental Component Summary at 6 mo was 2.2 (95% CI, -1.8 to 6.1; P = .28); treatment effect was significant for 5 of 63 secondary outcome measures: independent ADL completion at 6 mo, 1.0 (95% CI, 0.2 to 1.8), and at 12 mo, 0.9 (95% CI, 0.0 to 1.7; P = .3 and P = .05); XSMFA-F at 6 mo, -8.9 (95% CI, -17.0 to 0.7; P = .04); XSMFA-B at 6 mo, -9.9 (95% CI, -18.5 to -1.2; P = .03); Regensburg Insomnia Scale at 12 mo, -1.8 (95% CI, -3.5 to -0.1; P = .03)
<b>ICU Follow-up Clinics</b>									
Cuthbertson et al, <sup>79</sup> 2009	Scotland	286	>97% of adult ICU survivors received mechanical ventilation, median, APACHE II score, 19; median, ICU LOS, 3 d	Not reported	59	3-mo Self-directed physical rehabilitation and nurse-led intensive care follow-up clinic visits at 3 and 9 mo	Usual care	1 y	Estimated treatment effects (change in intervention minus change in control patients) were SF-36 Physical Component score at 12 mo, 1.1 (95% CI, -1.9 to 4.2; P = .46; SF-36 Mental Component score at 12 mo, 0.4 (95% CI, -3.0 to 3.7), P = .83. There was no significant treatment effect for any secondary outcome measures, including SF-36 at 6 mo; quality of life (EQ-5D) at 6 or 12 mo; anxiety (HADS-A) at 6 or 12 mo; or depression (HADS-D) at 6 or 12 mo
Jensen et al, <sup>80</sup> 2016	Denmark	386	Adult ICU survivors who received mechanical ventilation for at least 48 h, median, APACHE II score, 25; median, ICU LOS, 10 d	112 (29.0)	66	Nurse-led ICU Recovery Program, including an informational pamphlet, 1 clinic visit at 1-3 mo, and 2 telephone visits, at 5- and 10-mo post-ICU	Usual care	1 y	Estimated treatment effects (change in intervention minus change in control patients) were SF-36 Physical Component Score at 12 mo, 1.4 (95% CI, -1.5 to 4.4; P = .35); SF-36 Mental Component Score at 12 mo, 1.9 (95% CI, -1.1 to 4.9; P = .11); there was no significant treatment effects for any secondary outcomes at 3 or 12 mo, including anxiety (HADS-A), depression (HADS-D), PTSD (HTQ-IV), or sense of coherence (orientation to life scale)

Abbreviations and Definitions: Activities Balance and Confidence scale (range, 0%–100%) rates self-confidence in balance with higher scores reflecting greater confidence in balance; ADL, activities of daily living; ANOVA, analysis of variance; APACHE, acute physiology and chronic health evaluation; Dysexecutive Questionnaire is a self-reported measure of behavioral markers of executive function (score range, 0–80) with higher scores reflecting worse functioning; EQ-5D, EuroQol Five Dimensions Questionnaire; HADS-A, Hospital Anxiety and Depression Scale–Anxiety Subscale (range, 0–21) with higher scores representing greater anxiety; HADS-D, Depression Subscale (range, 0–21), with higher scores representing greater depression; Functional Activities Questionnaire is a 10-item self-report measure of complex instrumental activities of daily living (range, 0–30) with higher scores reflecting worse performance; HTQ-IV, Harvard Trauma Questionnaire; ICU, intensive care unit; IES, Impact of Event Scale (range, 0–88) with higher scores representing greater posttraumatic stress symptoms (PTSD) symptoms; IQR, interquartile range; LOS, length of stay; MMSE, Mini-Mental Status Examination, which assesses overall cognitive function (range, 0–30) with higher scores reflecting better function; SF-36, 36-Item Short Form Health Survey (range, 0–100) with higher scores represent greater quality of

life; Timed Up and Go test assesses ambulation ability, longer times reflect worse performance; Tower test assesses overall executive functioning ability on a test of planning and strategy (range, 1–19) with higher scores reflecting better performance; XSFMA-B, Extra Short Musculoskeletal Function Assessment regarding disability (range, 0–100) with higher scores represent greater impairment; XSFMA-E, function (range, 0–100) with higher scores represent greater impairment.

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