Long-term mortality and quality of life in sepsis: A systematic review

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Sepsis syndrome is a frequent cause of intensive care unit (ICU) admission and may also develop in patients admitted to the ICU for other reasons. In addition, the incidence of sepsis has increased over the past few decades (4) despite advances in supportive care, and the in-hospital case fatality rate for patients with sepsis remains high (1). Patients with sepsis are also at risk for complications such as acute lung injury (ALI) and multisystem organ failure (2, 3). Most clinical studies examining patients with sepsis have used 28-day mortality as a clinical end point. Because patients with sepsis may have complications with long-term sequelae, including critical illness weakness (5), delirium (6), and

LEARNING OBJECTIVES
After participating in this activity, the participant should be better able to:
1. Evaluate the impact of sepsis on long-term outcomes of patients.
2. Assess differences in mortality in septic patients at differing observation times.
3. Interpret the results of a systematic review of studies reporting long-term mortality and quality of life data in patients with sepsis.

Background: Long-term outcomes from sepsis are poorly understood, and sepsis in patients may have different long-term effects on mortality and quality of life. Long-term outcome studies of other critical illnesses such as acute lung injury have demonstrated incremental health effects that persist after hospital discharge. Whether patients with sepsis have similar long-term mortality and quality-of-life effects is unclear.

Objective: We performed a systematic review of studies reporting long-term mortality and quality-of-life data (>3 months) in patients with sepsis, severe sepsis, and septic shock using defined search criteria.

Design: Systematic review of the literature.

Interventions: None.

Main Results: Patients with sepsis showed ongoing mortality up to 2 yrs and beyond after the standard 28-day inhospital mortality end point. Patients with sepsis also had decrements in quality-of-life measures after hospital discharge. Results were consistent across varying severity of illness and different patient populations in different countries, including large and small studies. In addition, these results were consistent within observational and randomized, controlled trials. Study quality was limited by inadequate control groups and poor adjustment for confounding variables.

Conclusions: Patients with sepsis have ongoing mortality beyond short-term end points, and survivors consistently demonstrate impaired quality of life. The use of 28-day mortality as an end point for clinical studies may lead to inaccurate inferences. Both observational and interventional future studies should include longer-term end points to better-understand the natural history of sepsis and the effect of interventions on patient morbidities. (Crit Care Med 2010; 38:1276–1283)

Key Words: sepsis; mortality; quality of life; long-term; follow-up

*See also p. 1379.

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ALI (2, 3), the use of 28-day outcomes in clinical studies may underestimate the morbidity and mortality and may lead to inaccurate inferences. Sepsis alone, without these complications, may also have significant, unappreciated, long-term consequences secondary to effects on various organ systems, especially the central nervous system, by the pathogenetic mechanisms of the organism, the host's responses, or a combination of both.

There have been several studies highlighting the long-term outcomes in patients with ALI, of which a subset had sepsis as a risk factor (7–11). Herridge et al (12) demonstrated persistent functional disability (using the Short-Form 36 [SF-36] Quality of Life [QoL] instrument at 2 yrs after ALI) in survivors of ALI. These physical disabilities were most prominent in terms of muscle wasting and weakness (13). We therefore sought to perform a systematic review of the long-term mortality and QoL in patients with sepsis to better-understand long-term outcomes and to inform the design of clinical research.

MATERIALS AND METHODS

Search Strategy

To identify studies that measured mortality and/or QoL after hospital discharge in adult survivors of sepsis, severe sepsis, or septic shock, we searched MEDLINE (1966–2009), EMBASE (1974–March 2009), CINAHL (1982–2009), pre-CINAHL, and the Cochrane Library (2005–2009) as of March 1, 2009. The following search strategy was used, with all terms mapped to the appropriate MeSH/EMTREE subject headings and "exploded": ("Sepsis" [MeSH] OR "sepsis" [All Fields] AND ("follow up studies" [MeSH] OR "follow up studies" [All Fields] OR "health status indicators" [MeSH] OR "health status indicators" [All Fields] OR "quality of life" [MeSH] OR "quality of life" [All Fields]) No limits regarding language or publication type were applied. In addition, we hand-searched personal files, the reference list of narrative reviews, and all articles included in the final review.

Study Selection, Data Extraction, and Quality Assessment

Two authors (BDW, MHE) independently reviewed citations, abstracts, and full articles to select eligible studies. Any disagreement regarding eligibility of a full article was resolved by a third author (JES). Given the broad search criteria, we reviewed all titles as an initial screen looking for studies that would likely contain longitudinal data involving septic patients. Agreement between the two reviewers was calculated by percentage agreement and the kappa statistic. For foreign language articles, English translations of abstracts or the original articles were reviewed to determine eligibility. Original research studies were selected for review if they met all the following eligibility criteria: study of adults (age 18 yrs or older) with sepsis, severe sepsis, or septic shock and quantitative reporting of validated QoL or mortality data at least 90 days after ICU discharge.

Studies of other patient populations (e.g., critically ill patients in an ICU) were eligible only if they separately reported QoL or mortality data in sepsis, severe sepsis, or septic shock survivors. For each eligible study, two authors (BDW, MHE) independently abstracted data on study design, patient baseline characteristics (if available, such as gender, age, and comorbidities), mortality, study quality, and key exclusion criteria. Mortality data after hospital discharge were calculated using available data from either 28-day mortality or inhospital mortality until the last period of follow-up.

Study Quality

Study quality was assessed using three criteria adapted from the U.S. Preventive Services Task Force (14): (1) assessment of an inception cohort with longitudinal follow-up; (2) loss to follow-up of <25% over 1 yr; and (3) adjustment for confounders by randomization, statistical adjustment, or comparison to a matched population. No study was excluded from the synthesis based on the study quality assessment.

RESULTS

Search Results and Study Characteristics

We identified 11,733 citations using our search strategy. One hundred twenty-six abstracts and 53 full-text publications were chosen for review (Fig. 1). Thirty final articles met our inclusion criteria (Table 1). Reviewer agreement on selection of abstracts for full-text evaluation was 86% (κ = 0.73) and for inclusion of articles in the final review was 100% (κ = 1.0).

Total Mortality

Twenty-six studies provided data on long-term mortality from sepsis, with fol-
low-up ranging from 3 months to 10 yrs (15–40; Table 1), and 23 studies provided mortality data at least two time points (Fig. 2). Thirteen of these studies compared septic patients to a control population (15, 16, 19–24, 34, 38, 40, 42). Three of these were randomized, controlled trials (22–24) in which the controls were septic patients who did not receive treatment (activated protein C and antilipopolysaccharide Ab). Eleven studies used 1-yr end points (17, 18, 22, 23, 25–31), whereas eight reported end points <1 yr (up to 6 months) (19, 20, 24, 36–40) and seven reported end points >1 yr (15, 16, 21, 32–35). Total 1-yr mortality ranged from 21.5% to 71.9%.

### Mortality After Hospital Discharge

Twenty-three of the studies (15–17, 19, 22, 23, 25–40) provided data for 28-day mortality or inhospital mortality and mortality at a later time point, allowing us to determine a mortality after hospital discharge. We defined this mortality as the additional deaths after hospital discharge and/or 28 days compared to control group mortality (Fig. 3). Seventeen of these included a 1-yr follow-up. At 1 yr, mortality after hospital discharge ranged from 7% to 43% (Fig. 4). We were unable to determine individual length of stay in each study that used hospital discharge as their starting mortality rate. It is possible that hospital discharge for many patients was many weeks or months after their septic event and well beyond the 28-day mortality end point. Only one study, a...
long-term follow-up of the Prowess study (23), provided data on 28-day hospital discharge and long-term (2.5 yrs) mortality.

Eight studies that allowed for calculation of mortality after hospital discharge compared septic patients to a control population. The remaining 14 used an observational design (Table 1). Four of the controlled studies included at least a 1-yr end point. These studies reported mortalities after hospital discharge (septic vs. controls) of 22% vs. 8% (15), 7% vs. 2% (16), 25.6% vs. 13.2% (17), and 10% vs. 2% (18). These studies compared septic patients to noninfected patients, septic patients to critically ill noninfected trauma patients, septic pneumonia patients to nonseptic pneumonia patients, and a lupus patient who did or did not have sepsis develop, respectively. One study used a cohort design and provided 28-day or inhospital mortality and demonstrated a mortality of 9% after hospital discharge in the septic group vs. 8% in ICU patients without sepsis (19) at 6-mo follow-up. Two randomized, controlled trials (22, 23) of activated protein C vs. placebo both had similar mortality rate after hospital discharge at 1 yr of 15% and 17% without difference between the treatment and control groups.

The observational studies (25–41) ranged from 24 to 16,019 patients, with a follow-up duration from 3 mos to 10 yrs. One-year mortality after hospital discharge in eight studies providing these data, ranged from 11% to 42.5% (25–31). Three studies provided long-term mortality at end points beyond 1 yr (3–5 yrs), with mortality ranging from 21% to 54% (32–35) after hospital discharge. The patient population in these four studies varied widely, including human immunodeficiency patients (32), surgical patients (33), and mixed ICU patients (34, 35).

Six observational studies (36–41) provided mortality after hospital discharge over shorter time periods (3–6 mos). At

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**Table 1.** Mortality at Hospital Discharge after Sepsis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality at Hospital Discharge (%)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21%</td>
<td>Sasse et al. (1995)</td>
</tr>
<tr>
<td>2</td>
<td>31%</td>
<td>Quarin et al. (1997)</td>
</tr>
<tr>
<td>3</td>
<td>33%</td>
<td>Caulino et al. (1998)</td>
</tr>
<tr>
<td>4</td>
<td>7%</td>
<td>Haraldsen et al. (2002)</td>
</tr>
<tr>
<td>5</td>
<td>15%</td>
<td>Weycker et al. (2003)</td>
</tr>
<tr>
<td>6</td>
<td>7%</td>
<td>Falkenheuer et al. (2004)</td>
</tr>
<tr>
<td>7</td>
<td>12%</td>
<td>Lee et al. (2004)</td>
</tr>
<tr>
<td>8</td>
<td>15%</td>
<td>Angus et al. (2004)</td>
</tr>
<tr>
<td>9</td>
<td>16%</td>
<td>Braun et al. (2004)</td>
</tr>
<tr>
<td>10</td>
<td>13%</td>
<td>Laplante et al. (2005)</td>
</tr>
<tr>
<td>11</td>
<td>16%</td>
<td>Latore et al. (2007)</td>
</tr>
<tr>
<td>12</td>
<td>16%</td>
<td>Shapiro et al. (2007)</td>
</tr>
<tr>
<td>13</td>
<td>3%</td>
<td>Raggianni et al. (2008)</td>
</tr>
<tr>
<td>14</td>
<td>27%</td>
<td>Yende et al. (2009)</td>
</tr>
<tr>
<td>15</td>
<td>3%</td>
<td>Chen et al. (2009)</td>
</tr>
<tr>
<td>16</td>
<td>12%</td>
<td>Yang et al. (2009)</td>
</tr>
<tr>
<td>17</td>
<td>13%</td>
<td>Karlsson et al. (2009)</td>
</tr>
</tbody>
</table>

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**Figure 3.** Mortality after hospital discharge (%) at 3-, 6-, and 12-months and ≥2-yr time points for survivors of sepsis at 28 days or hospital discharge from 23 studies providing at least two mortality time points.

**Figure 4.** Mortality after hospital discharge (%) at 12 months in survivors of sepsis at 28 days or hospital discharge. Individual studies are arranged according to year of publication (first author, year of publication, and number of patients).
these shorter endpoints the mortality after hospital discharge is 5% at 3 mos (36), 11.3% at 5 mos (37), and 3% to 12% at 6 mos (38–41). The patient populations and numbers of patients varied widely in these studies, ranging from 24 to 1063 patients with either sepsis (37, 39) or severe sepsis (36, 38, 40), were limited to the Han population in one investigation (40), and were limited to an ICU population of patients treated with activated protein C (36) in another.

### QoL

Twelve studies provided QoL data using a variety of validated measures, including the EuroQol-5D (16, 19, 34) and the SF-36 (20, 24, 36, 38, 42, 43). Several studies used multiple scores (24, 42, 43, 45). Table 2 summarizes the QoL results.

Five studies, using the SF-36, demonstrated continued decrements in the patients’ QoL scores compared to population norms. Heyland et al (41) also compared sepsis to ALI and several noncritical chronic illnesses.

All three studies using the EuroQol-5D tool found decrements in QoL over the long-term. Granja et al (19) and Korosec et al (16) compared the EuroQol-5D in a septic cohort to other critically ill patients without sepsis, whereas Karlsson et al (34) compared sepsis patients with population norms. Of note, both Hofhuis et al (38), who used the SF-36, and Karlsson et al (34), using EuroQol-5D, found that their septic cohorts had a significantly decreased QoL before sepsis compared to the general population (Table 2).

### Study Quality

The selected studies had low to moderate study quality based on the U.S. Preventive Task Force criteria (Table 3). All

### Table 2. Study characteristics and QoL findings in adult sepsis survivors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>QoL Measure</th>
<th>Follow-Up, mos</th>
<th>Key Findings: QoL in Adult Sepsis Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perl et al (24)</td>
<td>1995</td>
<td>100</td>
<td>SF-36, Eastern Cooperative Oncology Group</td>
<td>6</td>
<td>RP, RE, PF, and GH were significantly diminished compared to population norms</td>
</tr>
<tr>
<td>Schelling et al (42)</td>
<td>1999</td>
<td>54</td>
<td>SF-36, posttraumatic stress disorder-10</td>
<td>120</td>
<td>No difference between septic patients treated with or without hydrocortisone</td>
</tr>
<tr>
<td>Heyland et al (41)</td>
<td>2000</td>
<td>30</td>
<td>SF-36, Patrick</td>
<td>16</td>
<td>(1) RP, RE, PF, and GH were significantly diminished in comparison to population norms; (2) PF worse in comparison to acute lung injury patients; other domains similar between groups; (3) GH and BP better compared with chronic obstructive pulmonary disease; other domains similar between groups; (4) no difference compared with congestive heart failure patients</td>
</tr>
<tr>
<td>Cook et al (36)</td>
<td>2004</td>
<td>24</td>
<td>SF-36</td>
<td>3</td>
<td>(1) RP, RE, and PF were significantly diminished in comparison to population norms; (2) no difference in comparison to non septic ICU patients</td>
</tr>
<tr>
<td>Longo et al (20)</td>
<td>2007</td>
<td>100</td>
<td>SF-36</td>
<td>6</td>
<td>All domains significantly diminished compared with population norms</td>
</tr>
<tr>
<td>Hofhuis et al (38)</td>
<td>2008</td>
<td>170</td>
<td>SF-36</td>
<td>6</td>
<td>(1) Presepsis event: RP, mental health, and BP significantly compared with population norms; (2) postsepsis event: reduced scores in all SF-36 dimensions except SF and BP compared with population norms</td>
</tr>
<tr>
<td>Granja et al (19)</td>
<td>2004</td>
<td>305</td>
<td>EuroQol-5D</td>
<td>6</td>
<td>Long-term decrements in QoL compared to nonseptic ICU patients</td>
</tr>
<tr>
<td>Korosec</td>
<td>2006</td>
<td>66</td>
<td>EuroQol-5D</td>
<td>24</td>
<td>Long-term decrements in QoL compared to nonseptic ICU patients</td>
</tr>
<tr>
<td>Karlsson et al (34)</td>
<td>2009</td>
<td>498</td>
<td>EuroQol-5D</td>
<td>24</td>
<td>(1) Presepsis event and postsepsis event: EuroQol sum and EuroQol Visual Analog Scale significantly lower compared with population norms; (2) postsepsis event: EuroQol sum significantly lower, EuroQol Visual Analog Scale unchanged in comparison to presepsis event in adult sepsis survivors</td>
</tr>
<tr>
<td>McLaughlan et al (43)</td>
<td>1995</td>
<td>125</td>
<td>WHO score</td>
<td>16</td>
<td>4 of 32 patients reported a poor QoL (no comparison population)</td>
</tr>
<tr>
<td>Haraldsen et al (33)</td>
<td>2002</td>
<td>210</td>
<td>Modified QoL score</td>
<td>72</td>
<td>Median scores were significantly compared with population norms; subjective assessment of QoL did not change significantly from preseptic values</td>
</tr>
<tr>
<td>Rublee et al (44)</td>
<td>2002</td>
<td>897</td>
<td>Karnosvky, Veterans’ Affairs</td>
<td>3</td>
<td>No difference between septic patients treated with or without antithrombin III</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; QoL, quality of life; SF-36, Medical Outcomes Study Short-Form 36-Item Health Survey; RP, physical role; RE, emotional role; PF, physical function; GH, general health; BP, bodily pain.
disorders, particularly in survivors of sepsis. Between 20% and 50% of patients have impaired QoL for at least 6 months after discharge from the hospital, and up to 20% of these patients have QoL impairment for up to 2 years after discharge. The impact of sepsis on QoL is not limited to patients who die from sepsis, as more than 10% of patients with severe sepsis or septic shock and 10% of patients with ALI have impaired QoL long after discharge from the hospital. Patients who survived their sepsis episode showed impaired QoL across different scales and patient populations compared to premorbid conditions, population norms, and critically ill patients without sepsis. It was interesting to note that an acute disease like sepsis showed similar decrements in QoL measures, over the long-term, compared to a chronic disease, such as chronic obstructive pulmonary disease or congestive heart failure, that are characterized by a cumulative disease burden.

**DISCUSSION**

Our study demonstrates that patients with sepsis of varying severity, including sepsis, severe sepsis, and septic shock, continue to die in the months and years after hospital discharge. Patients with sepsis also had additional decrements in QoL measures over the long-term. These results were consistent across varying severity of illness and different patient populations, including large and small trials, and across national borders with the clear direction toward increasing morbidity and mortality, although the actual magnitude varied from study to study. In addition, these results were consistent within observational trials and randomized, controlled trials.

These results are similar to those reported previously in patients with ALI (9). These results have broad implications for future clinical research studies. Many such studies tend to focus on end points at much shorter time points, typically at 28 days or hospital discharge, especially for mortality. It is becoming clear that such short-term end points do not reveal the ultimate effect of these conditions and are particularly without value for QoL, and other measures, such as the incidence of posttraumatic stress disorder, cognitive dysfunction, weakness (including conditions such as critical illness polyneuropathy), and chronic pulmonary dysfunction. We defined long-term outcome as >3 mos for the purposes of this systematic review, but there is no uniform definition for what constitutes a long-term outcome. Patients continue to have impaired QoL long after discharge.

Table 3. Study quality assessment using the U.S. Preventive Task Force Criteria

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N of Patients</th>
<th>Study Type</th>
<th>Inception Cohort With Longitudinal Follow-Up</th>
<th>Loss to Follow-Up &lt;25% Over 1 yr</th>
<th>Adjustment for Confounders by Randomization or Comparison to a Matched Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varty</td>
<td>1994</td>
<td>44</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>McLaughlin</td>
<td>1995</td>
<td>125</td>
<td>O</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Perl</td>
<td>1995</td>
<td>100</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sasse</td>
<td>1995</td>
<td>153</td>
<td>O</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sands</td>
<td>1997</td>
<td>1342</td>
<td>O</td>
<td>Yes</td>
<td>No (&lt;1 yr follow-up)</td>
<td>Yes</td>
</tr>
<tr>
<td>Quentin</td>
<td>1997</td>
<td>1505</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Casalino</td>
<td>1998</td>
<td>36</td>
<td>O</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Schelling</td>
<td>1999</td>
<td>54</td>
<td>C</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Heyland</td>
<td>2000</td>
<td>30</td>
<td>O</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Haraldsen</td>
<td>2002</td>
<td>210</td>
<td>O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rublee</td>
<td>2002</td>
<td>897</td>
<td>RCT</td>
<td>Yes</td>
<td>No (&lt;1 yr follow-up)</td>
<td>Yes</td>
</tr>
<tr>
<td>Yende</td>
<td>2003</td>
<td>16,019</td>
<td>O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Karlsson</td>
<td>2009</td>
<td>498</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

RCT, randomized, controlled trial; O, observational; C, observational study with control cohort.
fectively controlled for ALI; therefore, it is not possible to determine whether the long-term effects seen in our review are attributable to sepsis, ALI, or both.

Despite our inability to separate the attributable effects of sepsis or ALI, our results are consistent with those of other studies demonstrating long-term mortality after hospital discharge and impaired QoL secondary to a variety of serious illnesses. It is possible that our findings of long-term mortality after hospital discharge and impaired QoL may not be specific to an individual illness or syndrome but may be present in all forms of critical illness. Our results suggest that the traditional 28-day mortality outcomes used in clinical trials of sepsis, ALI, trauma, submersion injury, and many other critical illnesses requiring ICU-level care may underestimate the long-term sequelae of these syndromes and injuries. If our findings are correct, then future trials should include long-term outcome measurements, including mortality and QoL, to truly ascertain the full impact of this disease. Our results are also consistent with an increasing body of literature describing the long-term effects of critical illness in general, including neurologic and cognitive impairment (11, 48, 49), psychological symptoms (50–52), and QoL (38, 47). Finally, we find the results of Hofhuis (38) and Karlsson (34) noteworthy. Whereas Karlsson had a high loss to follow-up rate, both studies, using different QoL measurement tools (SF-36 for Hofhuis and Euro-QoL-5D for Karlsson), found that septic patients had lower QoL scores before discharge than did controls. Recently, interest in the human genetic susceptibility to infection has increased (53, 54). Similar findings were previously reported in critically ill patients with multisystem organ dysfunction syndrome (55, 56). These studies are not included here because they did not define a septic subgroup. It is possible that these observations of lower QoL before a septic episode, presumably attributable to a greater overall burden of illness or disability, have a link to susceptibility to infection.

There are several limitations to our study. First, the studies identified in this systematic review had study quality that was low to moderate. In addition, many of the studies would not fit the U.S. Preventive Task Force criteria for long-term end points. However, these studies provide additional information to the traditional 28-day mortality used in many critical illness studies. Second, we were able to provide a qualitative, but not quantitative, analysis of the study results. The mortality data did not allow for generation of an aggregate mortality curve (Kaplan-Meier). Despite contacting the authors of the SF-36 studies, we were unable to obtain adequate data to perform a quantitative analysis.

Despite these limitations, the signal from our qualitative analysis is clear. Mortality secondary to sepsis and its associated syndromes continues to increase long after the commonly used 28-day end point. Of note, Quartin et al (15) showed nearly three times the mortality after hospital discharge in septic patients at 1 yr compared to noninfected ICU patients. Because certain comorbidities might increase the risk for sepsis and mortality, such as diabetes, immunodeficiency, or hematologic disorders, all of which being statistically more common in the septic cohort, the attributable mortality of sepsis vs. the base comorbidities is difficult to know. However, Yende et al (17), who studied patients with community-acquired pneumonia with or without septic complications found a twofold increase in long-term mortality in the septic cohort. None of the studies effectively controlled for comorbidities when comparing to a control population.

A third limitation to our results centers around the lack of biomarkers for sepsis. Because other conditions such as noninfectious systemic inflammatory response syndrome may masquerade as sepsis, we cannot rule out the possibility of misclassification bias. Fourth, only some of the studies, which used population norms as controls, adjusted for expected age-related mortality over time. However, the observed mortality rates were far higher than we would expect from a healthy age-matched cohort. Further, we cannot determine which exposure during the septic events is causative for the observed long-term sequelae. Possible causes for the long-term impairments observed include hypoperfusion, toxins, maximal stress response (cytokines), exposure to treatments (such as steroids), immobility, development of complications such as ALI, or a combination of these or other factors. Finally, for mortality, we were unable to determine individual length of stay in the studies that used hospital discharge as their starting mortality rate. Because many patients may experience long hospital stays after their septic events (well beyond 28 days), censoring the data at 28 days may significantly underestimate the long-term effects because some patients die before hospital discharge. Thus, even the choice of short-term end points may have an effect on the inferences drawn from clinical studies. The wide range of “long-term” end points used in these studies in addition to variable start points for those mortality measurements underscore the need to develop more coherent guidelines for clinical research.

CONCLUSIONS

In conclusion, we found continued mortality after hospital discharge months and years after sepsis and impaired QoL in survivors of sepsis across a wide range of studies and patient populations. Future studies of sepsis should seek to systematically address the long-term sequelae and examine the independent contributions of sepsis, ALI, and other associated conditions to long-term outcomes.

REFERENCES


