The Lingering Consequences of Sepsis
A Hidden Public Health Disaster?

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SEPSIS, THE SYNDROME OF INFECTION COMPLICATED BY vital organ dysfunction, is a medical emergency that affects more than 750 000 patients in the United States each year and remains one of the world's leading causes of death.[1] Without prompt resuscitation, antibiotics, and institution of life support, patients can quickly develop shock, multisystem organ failure, and death. It is not surprising, therefore, that the main goal of care and of research has been to reduce short-term mortality. Assuming a patient survives the initial insult, traditional medical wisdom holds that the crisis has been averted and the patient should do well. However, this conventional thinking is being seriously challenged.

In 1997, Quartin et al[2] reported that sepsis survivors had double the risk of death in the following 5 years compared with hospitalized controls. Elderly patients and those with underlying disease have a higher risk of sepsis, and thus it seemed possible that this late increased mortality was unrelated to the sepsis episode but rather due to poor preexisting health condition. However, later studies that attempted more rigorous adjustment for preexisting conditions similarly found that survivors of sepsis had a long-term increased risk of death.[3,4] Other studies reported that sepsis survivors, and survivors of other related conditions, such as the acute respiratory distress syndrome, often developed physical, cognitive, and affective problems in the months and years after discharge.[5,6] There was no clear mechanism to explain these findings, which were broad and often nonspecific, and all these studies only initiated follow-up after the onset of the critical illness. Prospectively measured, detailed knowledge of function and health before the acute sepsis event was lacking, and thus the argument that underlying health status was the cause of subsequent decline could not be ruled out.

In this issue of *JAMA*, Iwashyna and colleagues[7] report the results of their study examining whether sepsis is associated with an increased risk of physical and cognitive impairment. To circumvent problems of prior studies, the investigators studied individuals in the Health and Retirement Study, a long-running cohort study of more than 27 000 older Americans, for whom they had detailed information on physical and neurocognitive function both before and after an episode of sepsis. The authors identified sepsis by screening all hospitalizations between 1998 and 2005 in the subset of participants for whom Medicare claims data were available. The diagnosis of sepsis is not easy to establish, especially using claims data. The authors used an existing diagnostic scheme that others have applied[1]; this approach is by no means perfect, but it identifies patients similar to those detected by prospectively trained clinical study coordinators.[1]

Once the patients were identified, Iwashyna et al[7] constructed models to predict how an individual patient's physical and cognitive function was affected by sepsis. This question is not trivial, and the answer could depend on the domain of physical or cognitive function measured, as well as whether the primary interest was in the magnitude or duration of any effect, in the absolute effect of sepsis, or simply in the marginal effect compared with the effect of hospitalizations in general. The authors approached the problem in several different ways and found consistent results: following sepsis, there was a significant increase in the odds of both physical and cognitive dysfunction that persisted throughout the 8-year follow-up. The new deficits were relatively more severe among patients who were in better health beforehand, possibly because there was less room for further deterioration among patients who already had poor physical or cognitive function prior to the sepsis episode. The magnitude of these findings was striking. For example, moderate to severe cognitive impairment increased 3-fold, from 6.1% before sepsis to 16.7% afterward. Extrapolating from national data, the authors estimated that sepsis may contribute to 20 000 new cases of moderate or severe cognitive impairment in the United States each year.

There are, however, important caveats. As with previous studies, the study design was observational—patients cannot be randomized to a bout of sepsis, and thus the inference is one of association, not causality. Furthermore, the exposure was a hospitalization during which sepsis occurred. Although patients who developed sepsis fared far

See also p 1787.

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worse than patients hospitalized generally, the authors cannot determine whether sepsis was the primary reason for subsequent deterioration, or whether the outcomes were due to other aspects of the patient's health or care precipitating or during the hospitalization in which sepsis occurred. In addition, the sample was relatively large but not large enough to explore, for example, whether the magnitude of the findings varied according to site and etiology of infection, magnitude of acute organ dysfunction, duration of intensive care unit (ICU) care, or use of different interventions. Moreover, patients who died before their postsepsis interview did not contribute to the analysis. These patients were probably more likely than those who survived to have dysfunction. Thus, their exclusion probably leads to an underestimate of the effects of sepsis on postdischarge outcomes. Finally, the study does not permit any interrogation of potential mechanisms to explain why sepsis would impair physical and cognitive function.

As the authors point out, there are a number of plausible explanations for their findings. Intensive care unit–acquired weakness, a constellation of myopathic and neuropathic syndromes, is well-described in sepsis and is thought to be due in part to muscle and nerve injury from inflammation, ischemia, and ischemia-reperfusion, pathways all implicated in the pathogenesis of sepsis.[8] Myopathy is further exacerbated by prolonged immobilization and use of certain drugs common in sepsis, such as corticosteroids and neuromuscular blockers. The brain is also susceptible to direct damage from inflammation, ischemia, and ischemia-reperfusion. Encephalopathy and delirium are both commonly described during the ICU care of patients with sepsis and are risk factors for dementia.[9] Inflammation may also be a direct cause of dementia.[10] In addition, many drugs used in the care of patients with sepsis and organ dysfunction potentially interfere with neurotransmitter and receptor pathways implicated in the development of neurocognitive impairment in other conditions such as schizophrenia and dementia.[11]

So, what are the important implications of the study by Iwashyna et al? First, the information in this study can help physicians when assessing care options and discussing outcomes with patients and families. Even if clinicians do not know why patients who develop sepsis experience a decline in function, it is clear that many patients do. Second, the development of preclinical models could help establish a better understanding of causality, potential mechanisms, and therapeutic targets. Current models of sepsis only crudely mimic sepsis in the modern ICU and rarely afford an assessment of long-term outcomes among survivors. Third, a number of relatively simple strategies used in other areas of medicine to promote physical rehabilitation and minimize the effects of neurocognitive dysfunction might be adaptable to the ICU and post-ICU setting and ought to be evaluated in clinical trials. Fourth, the traditional end point of day 28 all-cause mortality used in the evaluation of any therapy for sepsis should be replaced by longer-term survival data and functional outcomes. Assessing detailed physical and cognitive function is challenging and costly in the multicenter trial environment. However, the larger cost may be from failure to measure these outcomes and miss important benefits or harms of therapies on the lingering consequences of sepsis.

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REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
2. Quartin AA, Schein RM, Kett DH, Peduzzi PN; Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. Magnitude and duration of the effect of sepsis on survival. *JAMA*. 1997;277(13):1058-1063.
3. Kaplan V, Clermont G, Griffin MF, et al. Pneumonia: still the old man's friend? *Arch Intern Med*. 2003;163(3):317-323.
4. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc*. 2007;55(4):518-525.
5. Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
6. Angus DC, Carlet J; 2002 Brussels Roundtable Participants. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med*. 2003;29(3):368-377.
7. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
8. Schweickert WD, Hall J. ICU-acquired weakness. *Chest*. 2007;131(5):1541-1549.
9. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. 2004;14(2):87-98.
10. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol*. 2002;52(2):168-174.
11. Gray JA, Roth BL. Molecular targets for treating cognitive dysfunction in schizophrenia. *Schizophr Bull*. 2007;33(5):1100-1119.

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

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Context Cognitive impairment and functional disability are major determinants of caregiving needs and societal health care costs. Although the incidence of severe sepsis is high and increasing, the magnitude of patients' long-term cognitive and functional limitations after sepsis is unknown.

Objective To determine the change in cognitive impairment and physical functioning among patients who survive severe sepsis, controlling for their presepsis functioning.

Design, Setting, and Patients A prospective cohort involving 1194 patients with 1520 hospitalizations for severe sepsis drawn from the Health and Retirement Study, a nationally representative survey of US residents (1998-2006). A total of 9223 respondents had a baseline cognitive and functional assessment and had linked Medicare claims; 516 survived severe sepsis and 4517 survived a nonsepsis hospitalization to at least 1 follow-up survey and are included in the analysis.

Main Outcome Measures Personal interviews were conducted with respondents or proxies using validated surveys to assess the presence of cognitive impairment and to determine the number of activities of daily living (ADLs) and instrumental ADLs (IADLs) for which patients needed assistance.

Results Survivors' mean age at hospitalization was 76.9 years. The prevalence of moderate to severe cognitive impairment increased 10.6 percentage points among patients who survived severe sepsis, an odds ratio (OR) of 3.34 (95% confidence interval [CI], 1.53-7.25) in multivariable regression. Likewise, a high rate of new functional limitations was seen following sepsis: in those with no limits before sepsis, a mean 1.57 new limitations (95% CI, 0.99-2.15); and for those with mild to moderate limitations before sepsis, a mean of 1.50 new limitations (95% CI, 0.87-2.12). In contrast, nonsepsis general hospitalizations were associated with no change in moderate to severe cognitive impairment (OR, 1.15; 95% CI, 0.80-1.67; *P* for difference vs sepsis=.01) and with the development of fewer new limitations (mean among those with no limits before hospitalization, 0.48; 95% CI, 0.39-0.57; *P* for difference vs sepsis <.001 and mean among those with mild to moderate limits, 0.43; 95% CI, 0.23-0.63; *P* for difference=.001). The declines in cognitive and physical function persisted for at least 8 years.

Conclusions Severe sepsis in this older population was independently associated with substantial and persistent new cognitive impairment and functional disability among survivors. The magnitude of these new deficits was large, likely resulting in a pivotal downturn in patients' ability to live independently.

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COGNITIVE IMPAIRMENT AND physical disability are major health burdens and drivers of health care costs. The onset of disability is associated with worsened mortality[1] and substantial increases in medical costs over subsequent years,[2] including a disproportionate strain on Medicaid and Medicare. Both cognitive and physical disability impose yet further burdens on families and informal caregivers.[3] Irreversible cognitive and physical impairment following acute illnesses are particularly feared outcomes and weigh heavily on patient decision making.[4]

Hundreds of thousands of patients endure severe sepsis each year in the United States.[5] It has been suspected that many are discharged with a new—but poorly defined—constellation of cognitive and functional impairments,[6] which may explain their reduced quality of life.[7] Even hospitalizations for less severe illness often result in a period of functional disability[8] and may hasten the progression of dementia.[9,10] Long-term cognitive and functional declines have been shown among survivors of other critical illnesses, but these declines may be partially preventable.[11-14] Although severe sepsis is the most common noncardiac cause of critical illness,[5,15] the long-term impact of severe sepsis on cognitive and physical functioning is unknown.

See also p 1833 and Patient Page.

We studied whether an incident episode of severe sepsis increased the odds of subsequent worsened cognitive impairment and functional disability among survivors. We took advantage of a nationally representative ongoing cohort study of older Americans that included detailed information from personal surveys and

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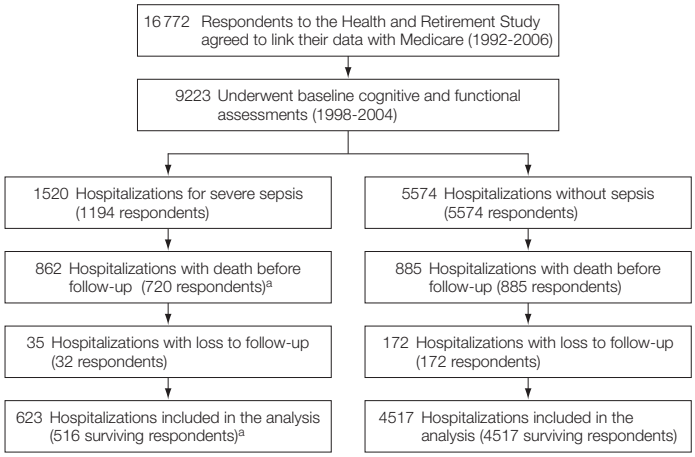
Figure 1. Patient Cohorts



[a] A single respondent with severe sepsis might contribute a hospitalization to the survivor cohort in one hospitalization but be lost to follow-up after a future hospitalization. The categorizations of hospitalizations as included vs excluded are mutually exclusive, but the categorizations of respondents are not. Comparisons were all first hospitalizations.

Medicare claims. This provided an opportunity to examine the long-term impact of severe sepsis before—and up to 8 years after—incident disease.

METHODS

Data Source

The Health and Retirement Study (HRS) is an ongoing cohort nationally representative of community-dwelling US residents older than 50 years. Begun in 1992, more than 27 000 individuals have contributed 200 000 hours of data-collection interviews. Every 2 years, the cohort is reinterviewed. The HRS achieved a very high follow-up rate, routinely exceeding 90% to 95% including proxies.[16] Furthermore, 16 772 participants have consented for linkage of their study data with Medicare.

This work was approved by the University of Michigan Institutional Review Board. Patients provided informed consent on enrollment in the HRS and again for linkage to Medicare claims.

We studied all respondents with at least 1 interview during 1998-2004 in which cognitive and physical functioning were assessed and for whom there were subsequent claims-based data on a hospitalization for severe sepsis during 1998-2005 (FIGURE 1). All patients were followed up through death or the 2006 survey. Our primary analyses focus on hospitalizations that patients survived long enough to participate in at least 1 follow-up interview.

Characteristics of the hospitalizations for severe sepsis were abstracted from the Medicare claims, including an organ dysfunction score (the sum of the number of organ failures of cardiovascular, neurologic, hematologic, hepatic, renal, or respiratory origin).[5,17] Self-reported race and ethnicity were included only in the descriptive statistics because they may be of interest to some readers.

Definition of Severe Sepsis

We relied on a claims-based definition of severe sepsis, which has been widely used and clinically validated.[5] This definition requires evidence of both an infection and new-onset organ dysfunction during a single hospitalization. If a patient had more than 1 distinct septic hospitalization, each hospitalization was included.

As a comparison, we conducted parallel analyses in a cohort of 5574 hospitalizations. These were first hospitalizations for members of the linked Medicare cohort, which included neither severe sepsis nor critical care use and for which a baseline survey and at least 1 follow-up interview were available.

Definition of Functional Status

At each wave of the survey, we asked respondents if they required assistance with any of 6 activities of daily living (ADLs: walking, dressing, bathing, eating, getting into and out of bed, and toileting) or 5 instrumental ADLs (IADLs: preparing a hot meal, shopping for groceries, making telephone calls, taking medicines, and managing money). We totaled the number of ADLs and IADLs to create a total deficiency score (range, 0 requiring no assistance to 11 requiring assistance for all categories).[18] The survey asked proxies to evaluate the functional status of patients who could not answer for themselves; proxies could answer these questions with high reliability.[18] For some analyses, a baseline of functioning was defined, using the last survey prior to severe sepsis. It was decided a priori that patients would be divided into 3 groups based on their baseline functioning: no limits, 0; mild to moderate, 1 to 3; and severe limitations, 4 or more deficiencies.

Definition of Cognitive Impairment

The survey assessed cognitive function in 2 ways during biennial personal interviews. For those aged 65 years or older, a 35-point scale was administered that included tests of memory, serial 7 subtractions, naming, and orientation.[19,20] For self-respondents younger than 65 years, the survey tool administered a more limited 27-point scale that excluded the orientation measures.

For patients 65 years or older who were unable to be interviewed themselves, the validated Informant Questionnaire on Cognitive Decline in the Elderly[21] was administered to proxies. For proxies representing respondents younger than 65 years, the following questions were used to determine cognitive function: "How would you rate [the respondent's] memory at the present time?" and "How would you rate [the respondent] in making judg-

ments and decisions?" The response options for both of these questions were excellent, very good, good, fair, or poor.

We defined cut points on the cognitive assessments for mild and moderate to severe cognitive impairment based on prior studies with the HRS data,[3,22,23] as well as the methods used for the Aging, Demographics, and Memory Study (ADAMS), a supplemental study of dementia in the HRS.[24] These cut points defined a level of cognitive impairment that was generally consistent with mild and moderate to severe dementia in the ADAMS. Further detail on the cognitive measures is available.[25]

Analyses

For analyses of functional status, our primary outcome was measured by a combined ADL and IADL score. For unadjusted analyses, we grouped patients by the number of surveys they had completed since severe sepsis occurrence; for example, we compared all patients at their last survey before hospitalization with severe sepsis with patients at their first survey after severe sepsis. For multivariable models, we used longitudinal models to examine the association between the timing of severe sepsis and the timing of functional changes. These models used only within-person variation over time in functional status to estimate the impact of severe sepsis, and thereby control for all characteristics of the patient that did not change over time—in essence, patients served as their own controls.[26] Specifically, we constructed latent growth curve models using a hospitalization-level fixed effect, sometimes called conditional models.[26] These results controlled for not only the functional status of the patient before his/her sepsis episode but also for functional trajectory. All of these sequential evaluations were included in the analysis. In these models, time from admission with severe sepsis to survey interview was measured to the day as a continuous variable. Additional information about the statistical approach is presented in the eMethods appendix, including alternative specifications (available at www.jama.com). Fixed effects models were estimated using *xtreg, fe* in Stata 10.1 (StataCorp LP, College Station, Texas). These analyses were not conducted according to a fully prespecified protocol.

For analyses of cognitive functioning, our primary outcome was level of cognitive impairment. Unadjusted analyses were conducted as for functional status. For multivariable analyses, we used conditional logistic regression to analyze the impact of severe sepsis on moderate to severe cognitive impairment among survivors, using *clogit* in Stata 10.1. As for functional status, these analyses used only within-person variation over time to estimate the effect of severe sepsis, controlling for time-invariant characteristics of the respondent.

All analyses were conducted with hospitalization as the unit of analysis unless otherwise indicated. Two-sided significance testing was used throughout, and a P value of .05 was considered statistically significant.

RESULTS

There were 1520 identified episodes of severe sepsis among 1194 respondents for the years 1998-2005, from a cohort of 9223 respondents (Figure 1). Detail about the entire population of severe sepsis hospitalizations is presented in eTable 1. Ninety-day mortality after severe sepsis was 41.3% (95% confidence interval [CI], 38.8%-43.8%); 5-year mortality, 81.9% (95% CI, 79.8%-84.0%). Five-year survival curves are presented in the eFigure (available at www.jama.com). Five hundred sixteen individuals survived 623 episodes of severe sepsis and had at least 1 follow-up survey; these hospitalizations by survivors are our primary cohort for analysis (TABLE 1). Patients were followed up for up to 4 surveys (7.8 years) of data prior to severe sepsis and up to 4 surveys (8.3 years) afterward.

Cognitive Outcomes

Incident severe sepsis was associated with a clinically and statistically significant increase in moderate to severe cognitive impairment among survivors. For example, 6.1% (95% CI, 4.2%-8.0%) of eventual survivors had moderate to severe cognitive impairment at the survey just before severe sepsis, and the prevalence increased to 16.7% (95% CI, 13.8%-19.7%) at the first survey after severe sepsis (FIGURE 2, $P < .001$ by χ^2 test). In fixed-effects regression, with each patient serving as his/her own control, the incidence of severe sepsis remained highly associated with progression to moderate to severe cognitive impairment (odds ratio [OR], 3.34; 95% CI, 1.53-7.25; TABLE 2). No association existed between severe sepsis and the net prevalence of mild cognitive impairment in adjusted or unadjusted analyses; nearly equal numbers of previously normal patients developed mild cognitive impairment after severe sepsis as patients with presepsis mild cognitive impairment developed postsepsis moderate to severe cognitive.

Functional Outcomes

Survivors of hospitalization for severe sepsis were at greater risk of additional functional limitations at their next survey. This was a substantial worsening in their trajectory relative to before their sepsis hospitalization. The negative effects of severe sepsis were greater in those patients with better baseline physical functioning (FIGURE 3). The new functional deficits were not concentrated in any particular subset of the functioning measures (FIGURE 4).

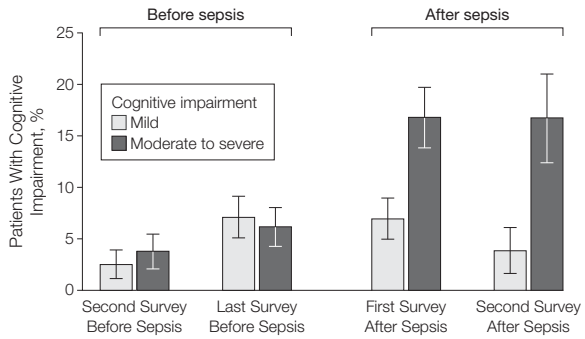
The independent effects of severe sepsis on long-term disability persisted in multivariable analyses with each patient's presepsis functional trajectory serving as his/her own control. TABLE 3 shows that severe sepsis was associated with the development of 1.57 (95% CI, 0.99-2.15) new limitations among patients who had none before sepsis. Patients with mild to moderate limitations before sepsis had a similar increase of 1.50 (95% CI, 0.87-2.12) new IADL and ADL limitations. For such patients, not only was sepsis

Table 1. Demographics of Study Cohort of Survivors, by Baseline Physical Functioning (n = 623)[a]

	Functional Class at Baseline by Limitations		
	None	Mild to Moderate	Severe
No.	269	195	159
Men, No. (%)	143 (53)	92 (47)	46 (29)
Race/ethnicity, No. (%)			
Black	49 (18)	41 (21)	38 (24)
Hispanic	19 (7)	12 (6)	13 (8)
Age at sepsis, mean (SD), y	75.8 (7.5)	76.7 (9.5)	79.1 (9.6)
Length of stay, mean (SD), d	11.4 (10.7)	11.3 (11.2)	8.5 (6.3)
Required mechanical ventilation, No. (%)	64 (23)	32 (16)	27 (17)
Required dialysis, No. (%)	9 (3.4)	6 (3.1)	12 (7.6)
Used an intensive care unit, No. (%)	137 (51)	75 (38)	57 (36)
Underwent major surgery, No. (%)	73 (27)	39 (20)	15 (9)
Charlson score, mean (SD)	1.69 (1.42)	1.96 (1.64)	2.11 (1.41)
Organ dysfunction score, mean (SD)	1.15 (0.39)	1.16 (0.45)	1.11 (0.34)
Acute conditions, No. (%)			
Cardiovascular dysfunction	60 (22)	62 (32)	45 (28)
Neurologic dysfunction	19 (7)	20 (10)	17 (11)
Hematologic dysfunction	61 (23)	34 (17)	27 (17)
Hepatic dysfunction	2 (1)	0 (0)	1 (1)
Renal dysfunction	103 (38)	79 (41)	60 (38)
Respiratory dysfunction	64 (24)	32 (16)	27 (17)
Baseline, No. (%)			
Cognitve impairment			
None	254 (94)	182 (93)	105 (66)
Mild	15 (5.6)	9 (4.6)	20 (12.6)
Moderate to severe	0	4 (2.1)	34 (21.4)
Physical function deficiencies, mean (SD)			
Basic ADL	0	1.3 (0.9)	4.0 (1.7)
Instrumental ADL	0	0.5 (0.7)	3.0 (1.5)
Proxy respondent, No. (%)			
At baseline	9 (3)	22 (11)	59 (37)
At first postsepsis survey	46 (17)	47 (24)	87 (55)

Abbreviation: ADL, activity of daily living.
[a] Data for the entire cohort of incident severe sepsis hospitalizations are in eTable 1, and risk factors for cognitive impairments are presented in eTable 2 (both available at www.jama.com).

Figure 2. Cognitive Impairment Among Survivors of Severe Sepsis at Each Survey Time Point



Error bars indicate 95% confidence intervals (CIs); IQR, interquartile range.
Interpretive Example: Compared with stable rates before severe sepsis, the prevalence of moderate to severe cognitive impairment increased from 6.1% (95% CI, 4.2%-8.0%) before severe sepsis to 16.7% (95% CI, 13.8%-19.7%) at the first survey after severe sepsis ($P < .001$ by χ^2 test; Table 2).

associated with an acute increase in the number of functional limitations, but sepsis also heralded a more rapid rate of developing further limitations thereafter, at 0.51 new limitations per year ($P = .007$ for difference vs baseline). In contrast, patients with already poor functioning experienced no statistically significant change in functioning with severe sepsis, although the regressions may be limited by ceiling effects in measurement of functioning.

Of the hospitalizations involving severe sepsis, 59.3% (95% CI, 55.5%-63.2%) were associated with worsened cognitive or physical function, or both, among survivors at the first postsepsis survey. The association of severe sepsis with increased functional limitations remained clinically meaningful and statistically significant in regression when controlling for changes in level of cognitive impairment after severe sepsis: 1.30 (95% CI, 0.86-1.74) new limitations for those with no limitations at baseline; 1.20, (95% CI, 0.62-1.79) new limitations for those with mild to moderate limitations at baseline. The increased risk of moderate to severe cognitive impairment remained clinically meaningful but was attenuated in the regressions when controlling for contemporaneous changes in levels of physical functioning after severe sepsis (OR, 1.73; 95% CI, 0.83-3.6).

Comparison to Other Hospitalizations

The changes in physical and cognitive functioning noted after severe sepsis were worse than those seen after nonsepsis general hospital admissions in a cohort of 4517 survivors of 5574 hospitalizations. Thus, patients who did not develop severe sepsis and who had no functional limitations prior to their hospitalization developed an average of 0.48 (95% CI, 0.39-0.57; n = 2852; P for difference vs sepsis $< .001$, eTable 3) new functional limitations. Patients with mild to moderate functional limitations at baseline developed 0.43 (95% CI, 0.23-0.63; n = 1124; P for difference = .001; eTable 3) new functional limitations after a nonsep-

sis general hospitalization. Furthermore, nonsepsis general hospitalizations were not associated with a clinically or statistically significant increase in the odds of moderate to severe cognitive impairment (OR, 1.15; 95% CI, 0.80-1.67; n=4517; *P* for difference=.01, eTable 4 available at www.jama.com)

Subgroup and Sensitivity Analyses

We replicated our analyses in several subgroups to examine their robustness. The effects of severe sepsis were similar in the 500 survivors who had severe sepsis but who did not require mechanical ventilation. The regression demonstrated similarly increased odds (OR, 4.0; 95% CI, 1.71-9.31) of developing moderate to severe cognitive impairment after severe sepsis among patients who were not mechanically ventilated. Similarly, in the 205 survivors with no limitations at baseline, severe sepsis without mechanical ventilation was associated with the development of 1.56 new functional limitations (95% CI, 0.91-2.22) in multivariable fixed-effects models. For the 163 patients with mild to moderate limitations, severe sepsis without mechanical ventilation was associated with 1.65 new functional limitations (95% CI, 1.01-2.28).

A potential threat to the validity of the results is that patients may have experienced some other cause of cognitive and functional decline between their baseline survey and their sepsis hospitalization. Therefore, we reanalyzed data for the smaller subset of 276 survivors who were never hospitalized between their baseline survey and their severe sepsis admission. We found consistent results, albeit with larger standard errors. In this subpopulation, severe sepsis was associated with increased odds of moderate to severe cognitive impairment (OR, 2.49; 95% CI, 0.99-6.26). In the 128 patients with no functional limitations at baseline and no intercurrent hospitalizations, severe sepsis was associated with the development of 1.46 new functional limitations (95% CI, 0.76-2.15). In the 86 patients with mild to moderate functional limitations at baseline and no intercurrent hospitalizations, severe sepsis was associated with the development of 1.34 new functional limitations (95% CI, 0.34-2.34).

Further sensitivity analyses yielded consistent results. The associations between severe sepsis and functional and cognitive impairment were substantively similar in those aged 65 years or older at baseline cognitive assessment and who therefore were assessed using a single instrument before and after severe sepsis (eTables 5 and 6). The patterns observed for functional limitations were similar in a larger cohort of 2043 hospitalizations (including 829 hospitalizations among 684 survivors) for severe sepsis followed up for up to 14 years during the period 1992-2006 (eTable 7). Examining only the subset of 516 first sepsis admissions for each survivor—so that no patient appeared in the analysis more than once—yielded nearly identical results (eTables 8 and 9).

COMMENT

In this nationally representative cohort, we have demonstrated for the first time that severe sepsis is independently associated with enduring cognitive and functional limitations. Severe sepsis is independently associated with a tripling in the odds of moderate to severe cognitive impairment. Furthermore, severe sepsis was indepen-

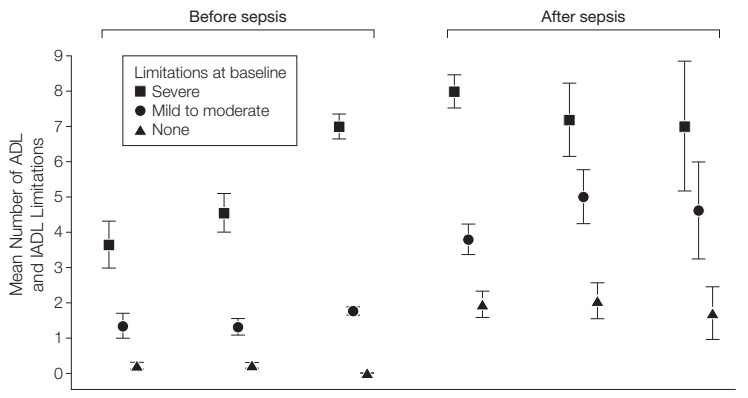
Table 2. Severe Sepsis and Moderate to Severe Cognitive Impairment Among Survivors[a]

	Odds Ratio (95% Confidence Interval)	*P* Value
Before sepsis (per additional year)	1.35 (1.11-1.65)	.002
Effect of sepsis	3.34 (1.53-7.25)	.002
After sepsis (per additional year)	1.68 (1.28-2.21)	.001

[a] Results of latent growth curve regression with individual-level fixed effects, controlling for all time-invariant characteristics of the patient. The absence of association would be indicated by an odds ratio of 1.

Interpretive Example: With each passing year, patients were modestly more likely to develop moderate to severe cognitive impairment. After severe sepsis, survivors had a 3.3-fold greater odds of having moderate to severe cognitive impairment than before sepsis (Figure 2).

Figure 3. Functional Trajectories by Baseline Functioning



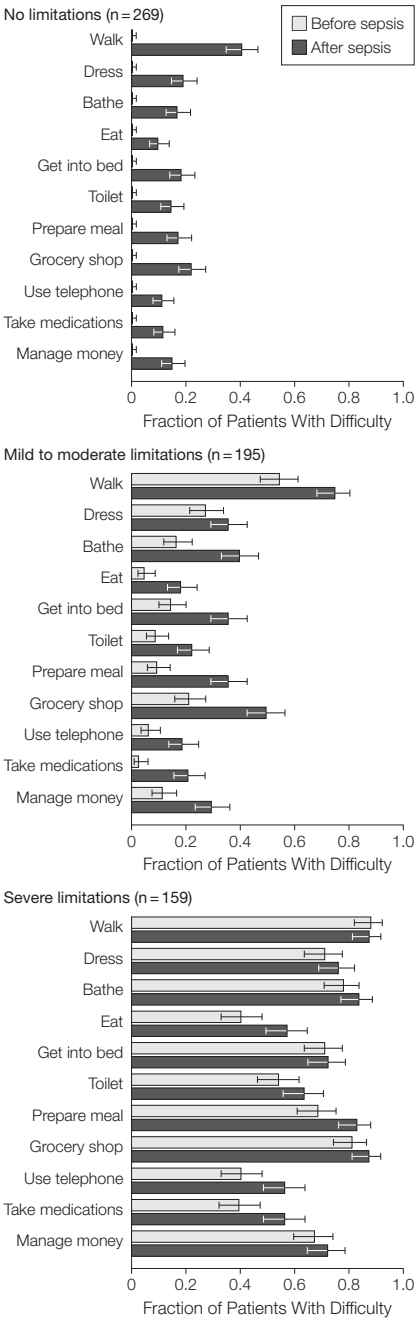
	Third Survey Before Sepsis	Second Survey Before Sepsis	Last Survey Before Sepsis	First Survey After Sepsis	Second Survey After Sepsis	Third Survey After Sepsis
Time to sepsis admission, median (IQR), y	–5.2 (–5.6 to –4.7)	–3.1 (–3.7 to –2.7)	–1.1 (–1.7 to –0.7)	0.9 (0.4 to 1.4)	2.8 (2.3 to 3.4)	5.2 (4.5 to 5.5)
No. of patients, by baseline physical functioning						
Severe limits	87	127	159	159	42	14
Mild to moderate limits	105	151	195	195	93	28
No limits	142	206	269	269	153	56

The unadjusted mean number of functional limitations of surviving cohort members is shown. Error bars indicate 95% confidence intervals.

Interpretive Example: Groups that had no functional or mild to moderate limitations before sepsis had a stable trajectory before sepsis but developed about 2 new limitations after sepsis. But patients with severe limitations at baseline had a modest increase from a baseline of 6.99 to 7.98 at their first survey after sepsis (Table 3).

dently associated with the acquisition of 1.5 new functional limitations in patients with no, mild, or moderate pre-existing functional limitations. These new disabilities were substantially larger than those seen after nonsepsis general hospital admissions. Cognitive and functional declines of the magnitude seen after severe sepsis are associated with significant increases in caregiver time, nursing home admission, depression, and mortality.[3,27-30] These data argue that the burden of sepsis survivorship is a substantial, underrecognized public health problem with major implications for patients, families, and the health care system.

Figure 4. Change in Individual ADLs and Instrumental ADLs by Baseline Functioning



Interpretive Example: No single activity of daily living (ADL) or instrumental ADL accounted for the worsened functional status among survivors of severe sepsis. Instead, there was a wide range of new difficulties across the array of activities.

Our findings, and the nationally representative data from the HRS, allow us to make an estimate of the overall public health burden of sepsis on "brain health" among older adults in the United States. Given published dementia[31] and sepsis[5] incidence rates for those aged 65 years or older in the United States, our results suggest that nearly 20 000 new cases per year of moderate to severe cognitive impairment in the elderly may be attributable to sepsis. Thus, an episode of severe sepsis, even when survived, may represent a sentinel event in the lives of patients and their families, resulting in new and often persistent disability, in some cases even resembling dementia.[3,22,32,33]

The level of severe cognitive impairment found in these patients has been associated with an additional 40 hours per week of informal care provided by families,[3] analogous to an additional full-time job. If causally related, this represents a substantial public health burden of accelerated or de novo brain dysfunction, and one that has received almost no attention, even in the face of the dramatically increasing incidence of severe sepsis.[15] In marked contrast to Alzheimer disease and some other forms of dementia, onset and acceleration of cognitive impairment due to sepsis is likely partially preventable in many patients. These benefits might be achieved by raising the standard of care for patients who develop sepsis—both sepsis-specific care as well as other intensive care unit practices such as sedation management and early physical and cognitive rehabilitation—and by avoiding sepsis altogether.[34] Improving the prevention and management of sepsis may warrant a place in the broader brain health and disability agendas.

Although an observational study can never prove causation, there are multiple plausible causal pathways by which sepsis and its treatment may lead to significant declines in physical and cognitive function. The literature on intensive care unit–acquired weakness and chronic illness myopathy and polyneuropathy suggests that there is a direct inflammatory and hypoperfusion-mediated degradation of muscle fibers and neurons,[35-37] which may be exacerbated by prolonged immobility[38] and lack of physical therapy.[39] Similarly, frank hypotension or relative hypoperfusion may directly contribute to brain injury and subsequent cognitive impairment.[40-42]

Inflammation—a cardinal component of the pathophysiology of sepsis—is hypothesized to contribute to both vascular dementia and Alzheimer disease.[6,10,43] Delirium, an acute form of brain dysfunction characterized by inattention, is common in sepsis, preventable, and treatable.[44,45] Delirium has been associated with increased cognitive decline among patients with Alzheimer disease[9,32] as well as with increased rates of long-term cognitive impairment in mechanically ventilated patients.[33] Basic biological research to understand these mechanisms is clearly warranted. Equally pressing is the need for innovative clinical trials of both sepsis-specific therapy and improved life support. Our results suggest that such trials should look beyond short-term mortality to long-term cognitive and functional outcomes of crucial interest to patients.[46]

We conducted analyses that address several possible limitations. The regressions used only within-person variation to estimate the association with severe sepsis; thus, characteristics of the survivors that did not change over time cannot explain the timing of changes in cognitive and functional status. The different cognitive and physical function out-

comes between the survivors of severe sepsis and of the comparison general hospitalizations suggest that the sepsis results were not simply due to the aging of the cohort or the mere fact of hospitalization, processes shared equally by both groups. These different outcomes also suggest that our results cannot be attributed solely to asymmetric censoring, one form of a potential bias known as "truncation by death."[47] However, because patients with worse cognitive and physical functioning have greater mortality (eFigure, available at www.jama.com),[22,30] there may be some conservative bias in our results. This form of truncation by death results if patients with the worst cognitive and physical declines after sepsis do not survive long enough for a follow-up survey. To the extent that such truncation by death is present, the full effect of severe sepsis on cognitive and physical functioning would be even greater than we measured.

Our study has several limitations. Unlike prior studies that have focused on acute functional decline in the perihospitalization period,[1,8,48-50] the present results demonstrate only long-term effects; short-term deficits (eg, less than 6-12 months) are likely greater, with at least some patients recovering some function prior to their next HRS biennial survey. The neuropsychological battery that we used provided an assessment of global cognitive function, but did not allow detailed study of individual cognitive domains nor did it establish a definitive clinical diagnosis of dementia. Importantly, we used cognitive categories and cutoff scores that have shown good correlation with clinical dementia[51] and expected outcomes of dementia[3,27] in prior studies. We used a claims-based definition of severe sepsis. Although this is not the same as prospective clinical assessment, it is the same approach used in recent landmark epidemiological studies.[5,15] Our data were restricted to fee-for-service Medicare patients aged 65 years or older.[5] We have shown that these deteriorations were temporally associated with severe sepsis and independent of other stable patient characteristics, but we have not conclusively proven that it was severe sepsis rather than other simultaneous events that led to these declines. Although, to our knowledge, this is the largest study to date of severe sepsis and our outcomes of interest, our study was not powered to examine interactions, such as the extent to which the changes after sepsis varied with the number of organ failures or type of inciting organism. Medicare claims lack the information necessary to disentangle whether particular acute interventions are associated with differing long-term outcomes. Finally, we demonstrated the association of severe sepsis with functioning under the treatment regimes in effect in a range of US hospitals at a particular point in time. New treatments for sepsis, or changes in life support or other hospital practices, may modify the long-term cognitive and functional effects of severe sepsis, even if these deficits are not an explicit target of care.

In summary, in this large nationally representative cohort of older adults, we found that the odds of acquiring moderate to severe cognitive impairment were 3.3 times as high following an episode of sepsis, with an additional mean increase of 1.5 new functional limitations per person among those with no or mild to moderate preexisting functional limitations. Thus, sepsis is often a sentinel event in the lives of older patients, initiating major and enduring cognitive and functional declines with lasting implications for patients' independence, for their loved ones, and for the societal institutions charged with supporting them. Future research to identify mechanisms leading from sepsis to cognitive impairment and functional disability—and interventions to prevent or slow these accelerated declines—is especially important now given the aging of the population.

Table 3. Acquisition of New Functional Limitations Before and After Sepsis Among Survivors by Functional Class at Baseline[a]

	Functional Class at Baseline by Limitations		
	None (n = 269)	Mild to Moderate (n = 195)	Severe (n = 159)
Before sepsis	−0.020	0.11	0.84
Per year, CI	−0.046 to 0.086	0.01 to 0.21	0.73 to 0.92
P value	.55	.03	<.001
Effect of sepsis	1.57	1.50	0.04
Per year, CI	0.99 to 2.15	0.87 to 2.12	−0.74 to 0.81
P value	<.001	<.001	.93
After sepsis	0.19	0.51	0.16
Per year, CI	−0.03 to 0.41	0.24 to 0.77	−0.19 to 0.50
P value	.09	<.001	.37

Abbreviation: CI, confidence interval.
[a] Results of latent growth curve regression with individual-level fixed effects, controlling for all time-invariant characteristics of the patient. The within-patient R^2 were 0.25 for the no limitation group, 0.37 for those with mild to moderate baseline limitations, and 0.45 for those with severe baseline limitations. The absence of association would be indicated by the acquisition of 0 new functional limitations.
Interpretive Example: Patients with mild to moderate limitations at baseline were acquiring 0.11 new limitations a year before severe sepsis. They acquired 1.50 new limitations at hospitalization for severe sepsis. Each year after sepsis, they acquired 0.51 new limitations a year, a statistically significant increase relative to their presepsis rates (Figure 3).

Author Contributions: Dr Iwashyna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Iwashyna, Ely, Langa.
Acquisition of data: Langa.
Analysis and interpretation of data: Iwashyna, Ely, Smith, Langa.
Drafting of the manuscript: Iwashyna, Ely, Langa.
Critical revision of the manuscript for important intellectual content: Iwashyna, Ely, Smith, Langa.
Statistical analysis: Iwashyna, Ely, Smith, Langa.
Obtained funding: Iwashyna.
Administrative, technical, or material support: Iwashyna, Ely, Langa.
Study supervision: Iwashyna, Ely, Langa.
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Online-Only Material: The eMethods appendix, eTables 1-9, and the eFigure are available at www.jama.com.

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REFERENCES

1. Rozzini R, Sabatini T, Cassinadri A, et al. Relationship between functional loss before hospital admission and mortality in elderly persons with medical illness. *J Gerontol A Biol Sci Med Sci*. 2005;60(9):1180-1183.

2. Fried TR, Bradley EH, Williams CS, Tinetti ME. Functional disability and health care expenditures for older persons. *Arch Intern Med*. 2001;161(21):2602-2607.

3. Langa KM, Chernew ME, Kabeto MU, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med*. 2001;16(11):770-778.

4. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med*. 2002;346(14):1061-1066.

5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.

6. Yende S, Angus DC. Long-term outcomes from sepsis. *Curr Infect Dis Rep*. 2007;9(5):382-386.

7. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.

8. Boyd CM, Landefeld CS, Counsell SR, et al. Recovery of activities of daily living in older adults after hospitalization for acute medical illness. *J Am Geriatr Soc*. 2008;56(12):2171-2179.

9. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology*. 2009;72(18):1570-1575.

10. Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology*. 2009;73(10):768-774.

11. Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.

12. Chelluri L, Pinsky MR, Donahoe MP, Grenvik A. Long-term outcome of critically ill elderly patients requiring intensive care. *JAMA*. 1993;269(24):3119-3123.

13. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171(4):340-347.

14. Kaarlola A, Tallgren M, Pettilä V. Long-term survival, quality of life, and quality-adjusted life-years among critically ill elderly patients. *Crit Care Med*. 2006;34(8):2120-2126.

15. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.

16. Health and Retirement Study. *Sample Sizes and Response Rates*; 2008 http://hrsonline.isr.umich.edu/sitedocs/sampleresponse.pdf. Accessed 27 October 2009.

17. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.

18. Fonda S, Herzog AR. *Documentation of Physical Functioning Measured in the Heath and Retirement Study and the Asset and Health Dynamics Among the Oldest Old Study*. Ann Arbor, Michigan: Survey Research Center; December 21, 2004.

19. Herzog AR, Wallace RB. Measures of cognitive functioning in the AHEAD Study. *J Gerontol B Psychol Sci Soc Sci*. 1997;52(spec No):37-48.

20. Welsh KA, Breitner JCS, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol*. 1993;6:103-110.

21. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr*. 2004;16(3):275-293.

22. Langa KM, Larson EB, Karlawish JH, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimers Dement*. 2008;4(2):134-144.

23. Alzheimer's Association *Early Onset Dementia: A National Challenge, a Future Crisis;* 2006. http://www.alz.org/national/documents/report_earlyonset_full.pdf. Accessed on August 26, 2010.

24. Langa KM, Plassman BL, Wallace RB, et al. The Aging, Demographics, and Memory Study: study design and methods. *Neuroepidemiology*. 2005;25(4):181-191.

25. Ofstedal MB, Fisher GG, Herzog AR Documentation of Cognitive Functioning Measures in the Health and Retirement Study; *2005*. http://hrsonline.isr.umich.edu/sitedocs/userg/dr-006.pdf. Accessed August 25, 2010.

26. Allison PD. *Fixed Effects Regression Models.* Thousand Oaks: Sage; 2009.

27. Banaszak-Holl J, Fendrick AM, Foster NL, et al. Predicting nursing home admission. *Alzheimer Dis Assoc Disord*. 2004;18(2):83-89.

28. Zivin K, Llewellyn D, Lang I, et al. Depression among older adults in the US and England [published online ahead of print April 9, 2010]. *Am J Geriatr Psychiatry*. doi: 10.1097/JGP.0b013e3181dba6d2.

29. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA*. 2002;287(16):2090-2097.

30. Mehta KM, Yaffe K, Langa KM, Sands L, Whooley MA, Covinsky KE. Additive effects of cognitive function and depressive symptoms on mortality in elderly community-living adults. *J Gerontol A Biol Sci Med Sci*. 2003;58(5):M461-M467.

31. Ziegler-Graham K, Brookmeyer R, Johnson E, Arrighi HM. Worldwide variation in the doubling time of Alzheimer's disease incidence rates. *Alzheimers Dement*. 2008;4(5):316-323.

32. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. 2004;14(2):87-98.

33. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38(7):1513-1520.

34. Saint S, Savel RH, Matthay MA. Enhancing the safety of critically ill patients by reducing urinary and central venous catheter-related infections. *Am J Respir Crit Care Med*. 2002;165(11):1475-1479.

35. Sharshar T, Bastuji-Garin S, Stevens RD, et al; Groupe de Réflexion et d'Etude des Neuromyopathies En Réanimation. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Crit Care Med*. 2009;37(12):3047-3053.

36. Callahan LA, Supinski GS. Sepsis-induced myopathy. *Crit Care Med*. 2009;37(10)(suppl):S354-S367.

37. Schweickert WD, Hall J. ICU-acquired weakness. *Chest*. 2007;131(5):1541-1549.

38. Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. *JAMA*. 2008;300(14):1685-1690.

39. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients. *Lancet*. 2009;373(9678):1874-1882.

40. Kuo H-K, Sorond F, Iloputaife I, Gagnon M, Milberg W, Lipsitz LA. Effect of blood pressure on cognitive functions in elderly persons. *J Gerontol A Biol Sci Med Sci*. 2004;59(11):1191-1194.

41. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. *JAMA*. 2004;292(23):2901-2908.

42. Mikkelsen ME, Lanken PE, Biester R, et al. Conservative fluide strategy is associated with neurocognitive deficits in survivors of acute lung injury. Paper presented at: American Thoracic Society; May 21, 2008; Toronto, ON.

43. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population. *Lancet Neurol*. 2005;4(6):371-380.

44. Sprung CL, Peduzzi PN, Shatney CH, et al; The Veterans Administration Systemic Sepsis Cooperative Study Group. Impact of encephalopathy on mortality in the sepsis syndrome. *Crit Care Med*. 1990;18(8):801-806.

45. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753-1762.

46. Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. *Ann Intern Med*. 2010;153(3):204-205.

47. McConnell S, Stuart EA, Devaney B. The truncation-by-death problem. *Eval Rev*. 2008;32(2):157-186.

48. Boyd CM, Ricks M, Fried LP, et al. Functional decline and recovery of activities of daily living in hospitalized, disabled older women. *J Am Geriatr Soc*. 2009;57(10):1757-1766.

49. Boyd CM, Xue QL, Guralnik JM, Fried LP. Hospitalization and development of dependence in activities of daily living in a cohort of disabled older women. *J Gerontol A Biol Sci Med Sci*. 2005;60(7):888-893.

50. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *J Am Geriatr Soc*. 2003;51(4):451-458.

51. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States. *Neuroepidemiology*. 2007;29(1-2):125-132.

In Reply: We agree with Dr Umhau's contention that our trial of DHA for the treatment of AD does not exclude the possibility that non-DHA components of fish, consumed over long periods of time, may have beneficial effects on the aging brain that were not detected in our trial. We elected to use DHA rather than fish oil or mixed omega-3 fatty acids because animal studies showed that DHA alone is sufficient to modify Alzheimer-like brain pathology in transgenic mouse models,[1,2] brain levels of EPA are exceedingly low, EPA has antiplatelet properties that might increase the risk of complications, and this strategy also avoided the risk of other ocean-borne contaminants in fish oil. However, we recognize that this strategy may have excluded potentially beneficial components of fish oil, including selenium and vitamin D, as well as EPA. With respect to EPA in particular, however, we have as-yet-unpublished data from this trial relevant to Umhau's hypothesis that DHA supplementation might actually "decrease the abundance of EPA": plasma levels of EPA increased from mean (SD) 0.86 (0.53) weight percent (wt%) at baseline to 1.83 (0.82) wt% at 18 months in participants who took DHA supplements, with no significant change in placebo-treated participants (0.78 [0.4] wt% at baseline and 0.67 [0.26] wt% at 18 months; $P < .001$). This is presumably due to retroconversion of DHA to EPA.[3,4]

We also agree that an 18-month trial cannot replicate lifelong dietary habits and recognize that the findings from this trial testing the therapeutic potential of DHA in patients with established AD cannot be generalized to exclude a role for omega-3 fatty acid consumption in the prevention of AD. We also agree that although long-term studies of whole foods may be impractical for a number of reasons, it is possible to design and conduct controlled trials of rational combinations of nutrients. A National Institute on Aging–funded placebo-controlled trial of the combination of fish oil plus lipoic acid in participants with mild to moderate AD is in progress (ClinicalTrials.gov identifier: NCT01058941).

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Quinn and Aisen reported being named as co-inventors on a patent for DHA for the treatment of Alzheimer disease in apolipoprotein E-ε4–negative individuals, which was filed in July 2009. Drs Quinn and Aisen were added as co-inventors in February 2010. Drs Quinn and Aisen have waived personal rights to royalties related to this patent.

1. Calon F, Lim GP, Yang F, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron*. 2004;43(5):633-645.
2. Green KN, Martinez-Coria H, Khashwji H, et al. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. *J Neurosci*. 2007;27(16):4385-4395.
3. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr*. 2006;83(6)(suppl):1467S-1476S.
4. Conquer JA, Holub BJ. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. *J Nutr*. 1996;126(12):3032-3039.

Cognitive and Functional Impairment After Severe Sepsis

To the Editor: Dr Iwashyna and colleagues demonstrated high rates of new-onset cognitive and functional impairments among elderly survivors of severe sepsis.[1] Converging evidence from human and preclinical studies suggests such consequences of sepsis may be associated with the effects of the immune system on the brain.

Proinflammatory cytokines (ie, interleukins and tumor necrosis factor) released as result of inflammation can reach the brain in a number of ways: via peripheral afferents (ie, the vagus nerve), entry through leaky circumventricular areas in the blood-brain barrier, or active transport.[2] Once in the brain, the cytokine signal stimulates microglia to secrete inflammatory mediators (ie, cytokines, chemokines, and proteases) from its monocytes and macrophages.[3] These local inflammatory mediators can affect neuronal function and synaptic plasticity by increasing oxidative stress and weakening astrocytic tight junctions.[3] They also increase metabolism and reuptake of neurotransmitters (ie, serotonin, noradrenalin, and dopamine) and stimulate the hypothalamic-pituitary-adrenal axis.[2] We believe this may explain the occurrence of a range of cognitive and affective problems observed in sepsis survivors. In healthy volunteers, immune activation has been shown to increase circulating cytokines, induce anxiety and low mood, and decrease cognitive performance.[4]

Both normal aging and neurodegenerative disease have been shown to prime the microglia to produce an exaggerated inflammatory response during activation of the peripheral innate immune system.[5] Central acetylcholine, which seems to exert inhibitory control over microglia, can be reduced in elderly patients if they use drugs with anticholinergic properties or have (incipient) dementia.[3] Elderly patients are prone to develop delirium, even after apparently innocuous infection.[3] In an experimental mouse model of neurodegenerative disease, transient systemic inflammation was associated with acute exacerbation of cognitive and motor impairments and rapid disease progression.[5] Taken together, these findings may advance understanding of short- and long-term cognitive and functional impairments observed among patients of sepsis and why elderly patients can be particularly vulnerable.

Research has now focused on possible pathways to control microglial activation, by (1) direct inhibition by minocycline, a tetracyclic anti-inflammatory agent; (2) peripheral blockade of cytokines by, eg, anti–tumor necrosis factor; or (3) augmentation of inhibitory cholin-

ergic control by cholinesterase inhibitors.[3] Minocycline has been shown to attenuate both microglial activation and behavioral changes following administration of an immune activating agent in mice.[3] More research in this area is required.

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1. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
2. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.
3. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet*. 2010;375(9716):773-775.
4. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58(5):445-452.
5. Cunningham C, Campion S, Lunnon K, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biol Psychiatry*. 2009;65(4):304-312.

In Reply: Our study demonstrated adverse long-term outcomes after severe sepsis. With a substantial body of preceding research,[1-3] we hope that this establishes the importance of identifying the mechanisms of long-term cognitive and physical outcomes of sepsis. We agree with Drs Khandaker and Jones that inflammation and brain interactions, neurotransmitter derangements, and prolonged systemic inflammation may be promising lines of mechanistic inquiry.[4,5] A full investigation of these mechanisms is needed that uses not just short-term surrogate end points but true long-term follow-up.

The correspondents suggest that severe sepsis may be a heterogeneous syndrome and that there may be interactions between that acute heterogeneity and differences in baseline patient physiology in affecting long-term outcomes. Our study and others have shown that there is substantial variability between patients in the extent to which they develop brain or body problems after severe sepsis.[3] We do not know what drives this variability. Our ignorance hinders both the design of therapeutic trials and clinicians facing the challenges of prognostication for individual patients.

Severe sepsis should be thought of not only as life-threatening but also as life-altering.[6] Interventional trials explicitly targeting these life-altering long-term outcomes of severe sepsis are essential, as Dr Angus suggested in his accompanying Editorial.[1] Future trials should not accept 28-day outcomes as sufficient. Real long-term patient-centered outcomes are needed to better inform decision making for patients, families, and care providers. Appropriate end points should include objective assessments of cognitive function and physical disability that are impaired after severe sepsis.

Survivors of severe sepsis have a great need for collaboration between molecular biologists, physicians who care for patients with sepsis, and social scientists with expertise in the measurement and evaluation of meaningful long-term outcomes.

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1. Angus DC. The lingering consequences of sepsis: a hidden public health disaster? *JAMA*. 2010;304(16):1833-1834.
2. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. *Crit Care*. 2010;14(1):R6.
3. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.
4. Yende S, Angus DC. Long-term outcomes from sepsis. *Curr Infect Dis Rep*. 2007;9(5):382-386.
5. Jackson JC, Hopkins RO, Miller RR, Gordon SM, Wheeler AP, Ely EW. Acute respiratory distress syndrome, sepsis, and cognitive decline: a review and case study. *South Med J*. 2009;102(11):1150-1157.
6. Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. *Ann Intern Med*. 2010;153(3):204-205.

