A Systematic Assessment of the Surviving Sepsis Campaign's Evidence Supporting the Care of Patients with Severe Sepsis on the Wards

To the Editor:

Severe sepsis is a common problem on the general hospital wards, where 32–50% of all cases receive their care (1). Despite an intense focus on improving the recognition and management of patients with severe sepsis and septic shock in emergency departments (EDs) and intensive care units (ICUs), the Surviving Sepsis Campaign (SSC) recently found that 32% of all patients enrolled in the campaign were initially diagnosed on the wards (2). In their most recent guidelines for the management of patients with severe sepsis and septic shock, the SSC stated that these recommendations could be applied to all patients, regardless of their location of care, specifically including those patients who receive all or part of their care on the general hospital wards (3).

Patients with severe sepsis on the wards may differ from those in the ED and ICU in important ways that, in turn, may alter their response to treatment. First, there is an intense selection bias imparted by the specialized care provided in ICUs, with many patients needing circulatory or respiratory support requiring ICU admission. Second, the specific infections leading to sepsis differ on the wards when compared with the ICU (1, 4). Third, patients with sepsis on the wards have different rates and distribution of organ failure (1, 4). The widespread improvement efforts of the SSC have helped to reduce overall sepsis mortality (2), regardless of the initial setting of care. However, patients initially diagnosed on the wards face higher mortality rates (2), while there remains a large fraction of patients with severe sepsis who are unrecognized by treating clinicians (5), many of whom likely receive their care on the wards.

Despite clear recommendations that the SSC Guidelines for Management of Severe Sepsis and Septic Shock be applied to patients on the wards (3), the strength of evidence supporting these recommendations for this heterogeneous population remains unknown. Therefore, we sought to systematically assess the supporting evidence cited in the SSC's 2012 guidelines for the inclusion of adult wards patients. We defined wards patients as those inpatients who were diagnosed with severe sepsis or septic shock but did not receive care in an ICU during that hospitalization; sepsis care for wards patients may have been initiated in the ED or as inpatients.

Methods

Two authors (S.G. and J.S.) reviewed SSC 2012 Recommendations A–E and G, the core wards-relevant recommendations on initial resuscitation (A), screening for sepsis and performance improvement (B), diagnosis (C), antimicrobial therapy (D), source control (E), and fluid therapy for severe sepsis (G), using a structured data abstraction tool. The remaining recommendations were excluded, as they either generally applied only to care delivered in the ED or ICU or were recommendations thought to have less effect on immediate outcomes (*see* Table E1 in the online supplement). Pediatric recommendations and references were not reviewed.

Every article cited within the text was reviewed for the following data: study design, total number of patients, site of recruitment, and number of wards patients who could be identified. We defined a wards patients as a population specifically identified as such by the study (i.e., cared for outside of the ED or the ICU) or a population subdivided into a non-critically ill cohort by investigators. If a patient ever required ICU-level care, or if we could not determine the clinical status of a study's population, the patients were categorized as critically ill. All randomized controlled trials (RCTs) not explicitly cited themselves but included in any meta-analysis cited by the guidelines were also specifically assessed for the same information.

Results

A total of 122 studies from 25 specific recommendations were explicitly evaluated (Table 1). No RCT cited in the SSC 2012 Recommendations A–E and G specifically included wards patients; five such trials included in cited meta-analyses did, however, totaling 1,129 wards patients. All five trials were in support of recommendation D-4b (duration of empiric antibiotics). The remaining 24 recommendations relevant for the care of wards patients with severe sepsis or septic shock did not include any wards patients in the RCTs in the supporting citations. Specifically, there were no wards patients in any study, randomized or observational, supporting the initial fluid resuscitation of patients with severe sepsis or septic shock. The administration of intravenous antibiotics within 1 hour for patients with severe sepsis and septic shock for patients on the wards was supported by only one observational study. After including observational studies and adjusting for duplicate citations, 82,514 total patients support the SSC recommendations for wards patients, of whom only 9,290 (11%) actually received their care on the wards, irrespective of study type.

Discussion

Despite severe sepsis and septic shock among patients on the wards being common (1, 2), mortal (1, 2, 6, 7), and underrecognized (4, 5), strikingly little of the supporting evidence guiding the care of wards patients included any evidence specific to this population. We found that of the 25 specific recommendations purported to apply to patients on the wards, only the duration of empiric antibiotics included any wards patients in a prospective clinical trial. There were no wards patients in any type of trial supporting the aggressive fluid resuscitation that is often a cornerstone of the care of patients with severe sepsis and septic shock.

The SSC has recently published evidence that high compliance with the SSC Resuscitation Bundle is associated with

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This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Table 1. Surviving sepsis campaign recommendations stratified by the presence of wards patients in the supportive evidence

No Wards Patients in Any Supporting Study *(n = wards patients/total patients in cited studies)*	Only in Observational Studies *(n = wards patients/total patients in cited studies)*	Randomized Controlled Trials and Observational Studies *(n = randomized controlled trial wards patients/observational study wards patients/total patients)*
Early goal-directed therapy with normalized lactate (A-2) *(n = 0/648)*	Early goal-directed therapy with goals (A-1) *(n = 5,258/35,121)*	Empiric combination antibiotics duration (D-4b) *(n = 1,129/1,627/11,852)*
Cultures drawn before antibiotics (C-1) *(n = 0/1,017)*	Screen for severe sepsis (B-1) *(n = 5,228/16,916)*	
Imaging to identify infectious source (C-3) *(n = 0/0)*	Quality improvement for sepsis (B-2) *(n = 30/3,039)*	
Reassessing antibiotic regimen (D-2b) *(n = 0/0)*	Invasive candidiasis assays (C-2) *(n = 120/599)*	
Empiric combination antibiotics initiation (D-4a) *(n = 0/551)*	IV Antibiotics within the first hour (D-1) *(n = 5,296/22,218)*	
Duration of antibiotic therapy (D-5) *(n = 0/0)*	Activity and penetration of antibiotics (D-2) *(n = 1,928/5,726)*	
No antibiotics in the systemic inflammatory response syndrome without infection (D-7) *(n = 0/0)*	Biomarkers (D-3) *(n = 0/3,297)*	
Source control (E-1) *(n = 0/201)*	Antivirals (D-6) *(n = 205/371)*	
Pancreatic necrosis (E-2) *(n = 0/124)*		
Intervention with least physiologic insult (E-3) *(n = 0/0)*		
Intravascular device (E-4) *(n = 0/0)*		
Crystalloids (G-1) *(n = 0/0)*		
No hydroxyethyl starch (G-2) *(n = 0/8,679)*		
Albumin (G-3) *(n = 0/6,997)*		
Initial fluid challenge (G-4) *(n = 0/0)*		
Hemodynamic improvement (G-5) *(n = 0/0)*		

lower mortality among patients diagnosed with severe sepsis or septic shock on the wards (2). Although these results make an argument that the current recommendations may improve outcomes on the wards, the SSC collaborative did not, until recently, focus their efforts on the recognition and management of this population.

Furthermore, because of the differences in mortality rates, phase of illness, infections, and organ dysfunctions, we cannot assume that the recommendations will work for all patients in this heterogeneous group (8, 9). For example, optimal fluid resuscitation strategies may differ in patients on the wards because of differences in prevalence of comorbidities such as renal failure or diastolic heart failure that may affect response to fluids; the likely differences in incidence of pulmonary capillary leak may also lead to differences in tolerance of large fluid volumes. Likewise, such wards patients are at lower overall risk for death, leading to systematic differences in the risk–benefit trade-offs of more aggressive therapies, potentially including invasive lines (8, 9). Because of this large evidence gap for the management of patients with severe sepsis and septic shock on the wards, prospective, randomized controlled trials are urgently needed to ensure we do not unwittingly do harm to this large, vulnerable population.

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Pulmonary Infection Caused by *Mycobacterium shinjukuense*

To the Editor:

The burden of pulmonary nontuberculous mycobacterial infection appears to be increasing worldwide. To date, more than 150 nontuberculous mycobacteria (NTM) species have been identified, and approximately 50 species have been newly described in just the last 8 years. We present a case of a patient infected with a recently discovered NTM named *Mycobacterium shinjukuense*, confirmed by 16S rRNA gene analysis of organisms recovered from bronchial lavage fluid.

Case Summary

A 73-year-old woman was referred to our hospital because of an abnormal chest radiograph. Computed tomographic (CT) imaging of the chest showed bilateral infiltrates, many of which appeared to be centered on peripheral airways. Multiple nodules and marked bronchiectasis were found in the middle lobe and lingula (Figure 1).

Expectorated sputum revealed acid-fast bacilli (AFB). A culture of the sputum grew a nontuberculous *Mycobacterium*, which was not otherwise identified. Bronchial lavage fluid obtained from the right lower lobe also stained strongly positive for AFB. A nontuberculous *Mycobacterium* isolated from the lavage fluid could not be identified by DNA–DNA hybridization; however, analysis of the 16S rRNA gene identified the NTM as *M. shinjukuense*.

M. shinjukuense is a novel nonchromogenic species of NTM that was isolated from a patient in the Shinjuku Ward, a central location of Tokyo, Japan, in 2004. It was first reported by Saito and colleagues (1) in 2010. As determined by a phylogenetic analysis concatenation of the 16S rRNA gene, β-subunit of RNA polymerase, and heat-shock protein 65, *M. shinjukuense* was classified into group III of the *Runyon* classification (2), which includes *Mycobacterium tuberculosis*, *Mycobacterium ulcerans*, and *Mycobacterium marinum*; however, *M. shinjukuense* does not fall within the *M. tuberculosis* complex.

As of February 2015, 21 cases of *M. shinjukuense* lung infection have been reported, including a case report written in English (3), another case report in Japanese (4), and 19 cases reported in abstracts presented at Japanese scientific meetings. Of the 21 cases, sex and age were available in 15 and 13 cases, respectively. The ratio of male to female patients was 1:2. The median age of the 13 patients was 63 years, ranging from a patient 18 years old to patients in their 90s. Chest computed tomography imaging reportedly showed cavitary lesions in six cases, bronchiectasis in fix cases, nodules in three cases, infiltrates in two cases, ground-glass opacities in one case, and pleural thickening in one case (some patients overlapped).

In the present study, the minimum inhibitory concentrations of isoniazid, rifampicin, and ethambutol for *M. shinjukuense* isolated from our patient were $\leq$0.2, $\leq$0.03, and $\leq$1.0 μg/ml, respectively. Accordingly, we treated our patient with combinations of isoniazid, rifampicin, and ethambutol. Repeat chest computed tomography imaging performed 5 months after initiation of treatment showed improvement in the radiographic infiltrates. Three of four

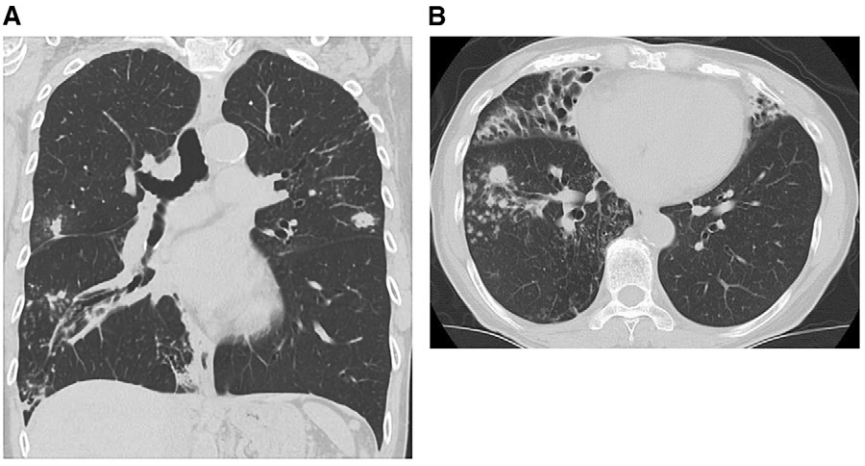

Figure 1. Representative coronal (*A*) and axial (*B*) chest computed tomography images showing the infection before onset of treatment.