Clinical Infectious Diseases

MAJOR ARTICLE

Infectious Diseases Team for the Early Management of Severe Sepsis and Septic Shock in the Emergency Department

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Background. The impact on patient survival of an infectious disease (ID) team dedicated to the early management of severe sepsis/septic shock (SS/SS) in Emergency Department (ED) has yet to be assessed.

Methods. A quasiexperimental pre–post study was performed at the general ED of our hospital. During the pre phase (June 2013–July 2014), all consecutive adult patients with SS/SS were managed according to the standard of care, data were prospectively collected. During the post phase (August 2014–October 2015), patients were managed in collaboration with a dedicated ID team performing a bedside patient evaluation within 1 hour of ED arrival.

Results. Overall, 382 patients were included, 195 in the pre phase and 187 in the post phase. Median age was 82 years (interquartile range, 70–88). The most common infection sources were lung (43%) and urinary tract (17%); in 22% of cases, infection source remained unknown. During the post phase, overall compliance with the Surviving Sepsis Campaign (SSC) bundle and appropriateness of initial antibiotic therapy improved from 4.6% to 32% ($P < .001$) and from 30% to 79% ($P < .001$), respectively. Multivariate analysis showed that predictors of all-cause 14-day mortality were quick sepsis-related organ failure assessment ≥2 (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.15–2.45; $P = .007$), serum lactate ≥2 mmol/L (HR, 2.13; 95% CI, 1.39–3.25; $P < .001$), and unknown infection source (HR, 2.07; 95% CI, 1.42–3.02; $P < .001$); being attended during the post phase was a protective factor (HR, 0.64; 95% CI, 0.43–0.94; $P = .026$).

Conclusion. Implementation of an ID team for the early management of SS/SS in the ED improved the adherence to SSC recommendations and patient survival.

Keywords. sepsis; septic shock; emergency department; infectious disease consultant; mortality.

Sepsis is a major public health concern worldwide, representing a leading cause of morbidity, mortality, long-term disability, and increased healthcare costs in developed countries [1, 2]. The incidence of sepsis continues to rise, reflecting both the increasing number of individuals at higher risk of severe infections (eg, elderly, immunosuppressed) and improved recognition [3, 4].

Prompt identification and appropriate treatment of severe sepsis and septic shock (SS/SS) are crucial to improving the patient outcome. Optimization of the management of patients with SS/SS in the emergency department (ED), which usually represents the first contact with the healthcare system for patients with community-onset sepsis, is a public health priority.

The Surviving Sepsis Campaign (SSC) promotes a bundle approach, with specific interventions (measurement of serum lactate level, drawing blood cultures, correct choice and administration of antibiotics, fluid resuscitation) to be completed in a timely manner [3]. In clinical practice, compliance with these recommendations may vary. It appears to be extremely difficult to adhere to SSC guidelines in EDs, especially with respect to microbiological work-up and prompt administration of the appropriate antibiotics [5–9]. Indeed, previous experiences in this setting have been mainly based on quick recognition of sepsis and fluid resuscitation protocols, with less attention given to microbiological work-up and choice of antibiotic therapy [10–12]. In the majority of cases, such interventions were based on educational activities and introduction of clinical decision-support tools [13–16]. The impact of the direct involvement of infectious diseases (ID) specialists in the care of patients with SS/SS attending the ED has yet to be assessed.

We hypothesized that implementation of an ID consultant service, available 24 hours per day/7 days per week, that provides early evaluation of patients with signs and/or symptoms of

Received 16 December 2016; editorial decision 2 June 2017; accepted 11 June 2017; published online June 12, 2017.

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Clinical Infectious Diseases® 2017;65(8):1253–9

DOI: 10.1093/cid/cix548

SS/SS in the ED would improve both diagnostic and antimicrobial management and eventually patient outcome. Therefore, our primary aim in this study was to assess the all-cause 14-day mortality in patients assessed for SS/SS at our ED before and after implementation of a dedicated ID team.

MATERIAL AND METHODS

Study Setting

The study was performed at the general ED of Sant'Orsola-Malpighi Hospital, a 1420-bed teaching hospital in northern Italy. It has a catchment area of 870 000 inhabitants and approximately 70 000 attendances per year.

Study Population

All consecutive adult (aged ≥ 18 years) patients who attended the general ED in a condition of severe sepsis or septic shock (SS/SS) from 1 June 2013 through 31 October 2015 were eligible for the study. Criteria of SS/SS were assessed at presentation according to a preestablished protocol based on 2012 SSC guidelines (see definitions below) [3] that were shared with all medical ED staff before study onset. Exclusion criteria were informed refusal, patients with do-not-resuscitate orders, and/or patients with a life expectancy of <72 hours.

Study Design

A quasiexperimental pre–post study was carried out. During the pre phase (June 2013–July 2014), patients with SS/SS were managed according to the following standard of care: the ED physicians were entirely responsible for patient management (microbiological work-up, fluid resuscitation, antibiotic therapy), with the possibility to ask for an ID consultation. During the post phase (August 2014–October 2015), patients with SS/SS were managed in collaboration with a dedicated ID team.

Patients were followed up until 30 days after admission. If they had been discharged or transferred to another healthcare facility earlier than 30 days from admission, data were collected by a telephone interview with patients, their relatives, or their physicians.

Intervention

A "sepsis team" (ST) made up of 13 ID specialists who belong to the ID unit of the hospital was created. ST members were available 24 hours per day, 7 days per week. They were notified when a patient with SS/SS was identified by the on-duty ED physician.

Intervention of the ST consisted of bedside patient evaluation within 1 hour of notification; recommendation for diagnostic work-up; prescription of antibiotic therapy (drug choice, daily dose, and schedule of administration); and indication for source control, if necessary.

During the post phase, compliance with the ST antimicrobial prescription was mandatory. In addition, ST members performed follow-up visits for all patients enrolled in the study. The first follow-up visit was scheduled 48–72 hours after evaluation in the ED to review antibiotic therapy and change it according to culture results, if necessary. Subsequent clinical assessments were performed based on the patient's clinical need.

Before starting the interventional phase, local guidelines for the management of patients with SS/SS were reviewed and updated by ST members (see Supplementary Material). During the post phase, ST members met weekly to review the cases of SS/SS enrolled in the study. To facilitate the adherence to microbiological work-up, a blood culture incubator for continuous monitoring was placed in the ED.

Ethics

Informed consent was obtained from eligible patients before enrollment. The study was conducted in accordance with the Helsinki Declaration and was approved by the hospital's institutional ethic committee.

Definitions

According to the criteria proposed by the 2012 SSC guidelines, severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion; septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [3]. Compliance with the SSC bundle was assessed according to lactate measurement, fluid resuscitation, drawing of blood cultures, and administration of antibiotics within 3 hours of ED admission [3].

An independent expert who was blinded to the study groups (pre and post phase) reviewed initial empiric antibiotic therapy at the end of the study, which was deemed as appropriate according to microbiological data, when available. In the others cases, the appropriateness was established according to the infection source and the presence of risk factors for difficult-to-treat pathogens (eg, patients coming from a nursing home or long-term care facility, patients hospitalized for more than 48 hours in the previous 90 days, patients on hemodialysis or intravenous therapy in the previous 30 days) [17].

Data

The following individual patient data were prospectively collected: demographics (age and sex); comorbidities according to the Charlson index; clinical severity (severe sepsis or septic shock); infection source; adherence to the SSC bundle; samples collected for etiological diagnosis and their results; antibiotic therapy, including time to administration of the first dose, drug choice, schedule of administration, changes in antibiotic therapy during hospitalization, and duration of antibiotic treatment; intensive care unit admission during hospitalization; length of stay; discharge to long-term care facility; and all-cause mortality.

Endpoints

Considering that among patients with SS/SS the majority of deaths occur within 14 days from diagnosis [18] and assuming that prompt and appropriate management of sepsis in the ED could have an impact in a short time, we set up all-cause

14-day mortality as the primary endpoint in order to minimize confounding events that could have occurred later during the hospital stay [19]. Secondary endpoints were compliance with all items in the SSC bundle, attempt to etiological diagnosis, proportion of patients with documented causative agents, and appropriateness of initial empiric antibiotic therapy.

Statistical Analyses

Based on the literature, we expected an all-cause 14-day mortality to range from 35% to 40% [18, 20–22]. Our hypothesis was that, with intervention, we would observe a reduction of about 10%. Thus, accepting a power of at least 80% and an alpha error of 5%, we calculated a sample size of 180 patients per period.

Descriptive statistics were obtained for all variables assessed in the study population. Mean and standard deviation were used for normally distributed continuous variables, median and interquartile ranges were used for skewed distributions, and proportions were used for categorical variables.

The pre and post phases were compared. Differences were tested with parametric or nonparametric tests for quantitative variables according with their distribution and with Pearson χ^2 or Fisher exact test, as appropriate, for categorical variables.

To assess risk factors for 14-day mortality, univariate and multivariate Cox regression analysis was carried out. All variables with a P value ≤ .1 at univariate analysis were entered into the multivariable Cox regression model. Statistical significance was considered for P values < .05. Analyses were carried out with SPSS 22.0.

RESULTS

During the study period, there were 172 577 general ED attendances. In 12 483 cases, the patient left the ED before medical evaluation, leaving 160 094 patients available for assessment.

A total of 436 patients were diagnosed with SS/SS, 216 in the pre phase and 220 in the post phase. In the pre phase, 5 patients were excluded because they declined to participate and 16 were excluded because life expectancy was less than 72 hours. In the post phase, 10 patients were excluded because they declined to participate and 23 were excluded because life expectancy was less than 72 hours. The study flow chart is showed in Figure 1.

Demographic and clinical characteristics of the study population are summarized in Table 1. Briefly, half of patients were males, median age was 82 years (interquartile range [IQR], 70–88), and the median Charlson comorbidity index was 6 (IQR, 5–8). The most frequent sources of infection were lung (43%) and urinary tract (17%); in 22% of cases the infection source remained unknown.

Comparison Between Pre and Post Phases

Comparison between patients enrolled in the pre and post phases is shown in Table 1. Significant differences were found for median age (84 vs 80 years, P = .008), median Charlson index (7 vs 5, P < .001), and septic shock rate (7.2% vs 17.6%, P = .002).

During the pre phase, the ED physicians asked for an ID consultation in only 15 cases. In all cases the compliance with ID advice was complete. All-cause 14- and 30-day mortality rates in patients with and without ID advice in the pre phase were 13% vs 41% (P = .06) and 26% vs 47% (P = .30), respectively.

Compliance with the items of the SSC bundle significantly improved between pre and post periods in terms of lactate measurement (76% vs 90%, P < .001), fluid resuscitation (56% vs 70%, P = .004), drawing blood cultures (20% vs 84%, P < .001), and administration of the first antibiotic dose within 3 hours of ED admission (43% vs 58%, P = .03).

The distribution of infection sources was similar between the 2 groups. Etiological diagnosis was reached more frequently in the post phase (9% vs 42%, P < .001). Overall, the most frequent pathogens were *Enterobacteriaceae* (46 cases), *Streptococcus pneumoniae* (11 cases), and *Staphylococcus aureus* (9 cases). Notably, 4 candidemia and 3 bloodstream infections caused by carbapenem-resistant *Klebsiella pneumoniae* were identified.

Use of appropriate empiric antibiotic therapy (30% vs 79%, P < .001) and switch to targeted therapy (13% vs 43.6%,

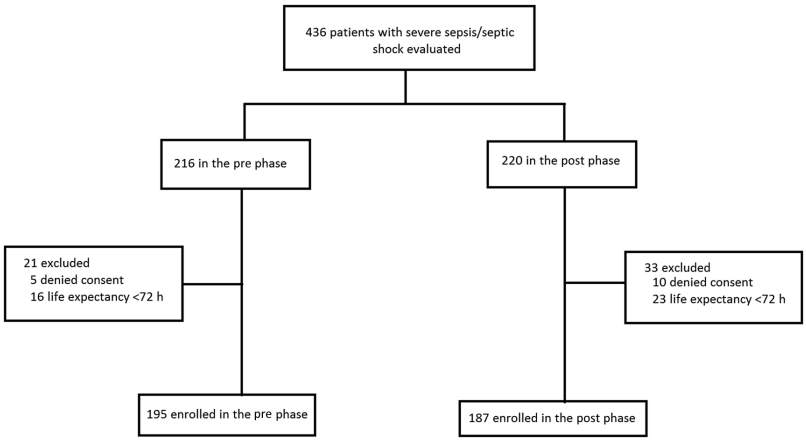

Figure 1. Flow chart of study population.

Table 1. Characteristics of Study Population and Comparison Between Pre and Post Phases

Characteristic	All Patients (N = 382)	Pre Phase (N = 195)	Post Phase (N = 187)	*P* Value
Age (y), median (IQR)	82 (70–88)	84 (73–89)	80 (67–87)	.009
Age class (y), no. (%)				
18–64	59 (16)	24 (12)	35 (19)	.015
65–84	169 (44)	79 (41)	90 (48)	
≥85	154 (40)	92 (47)	62 (33)	
Male sex, no. (%)	190 (49.7)	97 (49.7)	93 (49.7)	.998
Charlson index, median (IQR)	6 (5–8)	7 (6–8)	5 (4–7)	<.001
Preadmission antibiotics	118 (31)	63 (32)	55 (29)	.540
Infection site, no. (%)				
Lung	164 (43)	75 (38.5)	89 (48)	.317
Urinary tract	67 (17)	41 (21)	26 (14)	
Intraabdominal	30 (8)	14 (7)	16 (9)	
Skin and soft tissue	20 (5)	11 (5.5)	9 (5)	
Other sites	18 (5)	7 (4)	11 (4.8)	
Unknown	83 (22)	47 (24)	36 (19.2)	
Systemic inflammatory response syndrome criteria, no. (%)				
Body temperature >38.3°C or <36°C	128 (33.5)	72 (37)	56 (30)	.149
Heart rate >90 bpm	218 (56.5)	112 (57)	106 (56)	.879
Respiratory rate >20/min	145 (38)	66 (34)	80 (43)	.091
White blood cell count >12c000/mmc or <4000/mmc	254 (66.5)	126 (65)	128 (68)	.427
Altered mental status, no. (%)	141 (37)	76 (39)	65 (35)	.393
Serum lactate >2 mmol/L, no. (%)	237 (62)	106 (54)	131 (70)	.002
Septic shock, no.(%)	47 (12)	14 (7)	33 (17.6)	.002
Compliance with Surviving Sepsis Campaign bundle, no. (%)	68 (17.8)	9 (4.6)	59 (32)	<.001
Fluid resuscitation	240 (63)	109 (60)	131 (70)	.004
Lactate measurement	317 (83)	148 (76)	169 (90)	<.001
Antibiotics <3 hours from admission	191 (50)	82 (42)	109 (58)	.002
Blood culture before antibiotics	198 (52)	40 (20.5)	158 (84.5)	<.001
Unit of admission after the ED evaluation, no. (%)				
Intensive care unit	213 (56)	93 (48)	120 (64)	.001
ED ward	57 (14.9)	52 (26.7)	5 (2.7)	<.001
Medical ward	113 (29.6)	52 (26.7)	61 (32.6)	1
Surgical ward	13 (3.4)	6 (3.1)	7 (3.7)	1
Etiological diagnosis, no. (%)	97 (25)	18 (9)	79 (42)	<.001
Appropriate empiric antibiotic therapy, no. (%)	206 (54)	58 (30)	148 (79)	<.001
Time to first antibiotic dose (min), median (IQR)	164 (96–245)	169 (86–301)	154 (101–232)	.42
Time to appropriate antibiotic dose (min), median (IQR)	153 (101–235	180 (112.25–295.75)	146 (100–232)	.04
Changes in antibiotic therapy, no. (%) Reason for changes	196 (51)	86 (44)	110 (59)	.004
Deescalation with microbiological data	59 (30)	11/86 (13)	48/110 (43.6)	<.001
Deescalation without microbiological data	33 (17)	15/86 (17.4)	18/110 (16.2)	.993
Clinical failure	41 (21)	22/86 (25.5)	19/110 (17.2)	.214
Adverse event	3 (1.5)	1/86 (1.1)	2/110 (1.8)	1
Unknown	60 (30.5)	37/86 (43)	23/110 (21)	.001
Length of antibiotic therapy (days), median (IQR)	10 (4–15)	8 (3.5–13.5)	11 (6–19)	.002
Length of stay (days), median (IQR)	9.5 (3–17)	7 (2–13.5)	12 (6–21)	<.001
All-cause 14-day mortality, no. (%)	130 (34)	77 (39)	53 (29)	.02
All-cause 30-day mortality, no. (%)	157 (41)	88 (45)	69 (37)	.102
Discharged to long-term-care facility, no. (%)	60 (29)	35 (36)	25 (23)	.04

Abbreviations: ED, emergency department; IQR, interquartile range.

$P < .001$) were performed more frequently during the post phase. However, median length of therapy (8 vs 11 days, $P = .002$) and median length of stay (7 vs 12 days, $P < .001$) were longer during the post phase. In addition, we observed an increase in the costs of hospitalization between pre and post phases, from 5120 € per patient enrolled during the pre phase to 6745 € per patient enrolled during the post phase, on average.

Analysis of All-Cause Mortality

Overall, 130 patients (34%) died within 14 days of ED admission. Nonsurvivors were older than survivors and had a higher

Charlson index. Mortality was higher among patients in whom the infection site remained unidentified (55%) and lower in those with skin and soft tissue infections (20%). Mortality rates were 32% in patients with pneumonia, 22% in those with urinary tract infections, 23% in those with intraabdominal infections, and 27% in those with infections at other sites.

During the pre phase, 39% of patients died within 14 days of ED admission; this proportion decreased to 29% during the post phase ($P = .02$). In the 47 patients with septic shock, the all-cause 14-day mortality rates were 57% in the pre phase and 51% in the post phase ($P = .76$). In the 164 patients with pneumonia, the all-cause 14-day mortality rates were 37% in the pre phase and 28% in the post phase ($P = .24$).

Univariate and multivariate analysis of risk factors for all-cause 14-day mortality were performed (see Table 2). At multivariate analysis, predictors of all-cause 14-day mortality were quick sepsis-related organ failure assessment ≥2 (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.15–2.45; $P = .007$], serum lactate ≥2 mmol/L (HR, 2.13; 95% CI, 1.39–3.25; $P < .001$), and unknown source of infection (HR, 2.07; 95% CI, 1.42–3.02; $P < .001$). Being managed in collaboration with the ST was a protective factor (HR, 0.64; 95% CI, 0.43–0.94; $P = .026$) (see Table 2).

DISCUSSION

Here, we describe a novel approach to the management of patients with SS/SS cared for in the ED. This model, which is based on early bedside involvement of an ID specialist, was effective in reducing 14-day mortality by improving not only the approach to microbiological work-up and antimicrobial administration but also compliance with all items in the SSC bundle and the further patient care.

Regarding the epidemiological characteristics of our study population, it is important to note the higher proportion of elderly patients compared with prior studies on SS/SS in the ED; median age 82 years vs 60–65 years in other series and clinical trials [6, 23–26]. This discrepancy is likely explained by the demographic characteristics of the Italian population and the way EDs are used in our country. Indeed, a recent population-based study on the use of EDs in a northern Italian region showed that 38% of patients were aged >65 years, while in studies from other countries the proportion was between 12% and 24% [27, 28]. Thus, also our study underlines the issue of elderly management in EDs, for which some authors have suggested a dedicated geriatric ED unit or a strict interrelation between geriatric staff and ED organization [29].

Literature on community-onset SS/SS indicates the lung as the most frequent source of infection, followed by the urinary tract [23, 24, 26, 30–32]. These findings are confirmed in our study. We also encountered a high proportion (22%) of patients in whom the infection source remained unidentified; the high proportion of older patients who usually present with atypical symptoms may partially explain this figure. In addition, the unknown infection source was associated with a high risk of 14-day mortality. A trend toward higher mortality, not confirmed by multivariate analysis, has been reported for patients with unknown sources of infection in 2 recent European studies on SS/SS [31, 32]. We hypothesize that in such cases, the unfeasibility to achieve an adequate source control and to choose an antibiotic regimen with a specific pharmacokinetic target could negatively affect the outcome. Since a recent review concluded that reliable data on the impact of infection source on mortality in patients with SS/SS are scant [33], our study adds information about this topic.

Despite older age, comorbidities and difficulties in identifying the infection source were independently associated with mortality; intervention of the ST was a significant protective factor. The improved use of microbiological resources (with higher rate of etiological diagnosis) and of antimicrobials was very favorable. Indeed, during the post phase, we observed a significant increase in the drawing of blood for cultures (+64%) and in the timely administration of appropriate antibiotics (+49%), which are the most critical items in the SSC bundle to implement in EDs [9]. Notably, the practice of deescalation according to etiological diagnosis increased by 30.6%. All of these items can contribute to a virtuous cycle aimed to optimize both diagnostic approach and antimicrobial use, which are the cornerstones of every antimicrobial stewardship program [34, 35].

Consistent with other studies that have addressed different patient populations, types of infection, and causative microorganisms, we found that the bedside availability of an ID consultant was associated with improved patient outcome [36–39]. It remains to be determined why in some experiences, including ours, treatment duration, length of hospital stay, and costs increased when the ID specialist was involved. Increased survival likely plays a pivotal role, especially in an aged population like ours, where the acute infective episode may entail an important deterioration of the general status and worsening preexisting comorbidities.

The strengths of our study are the relatively large sample of patients included in both periods, the prospective collection of data, and the real-life perspective. However, our study has limitations. Being a single-center study, the external validity should be confirmed. Our study population consisted largely of elderly patients with multiple comorbidities. Consequently, the impact of the intervention could be different, even better, in a younger patient population. Because the definition of attributable mortality in septic patients is a matter of debate and its assessment may be difficult, especially in elderly patients with multiple comorbidities, we chose all-cause 14-day mortality as the primary endpoint. However, we followed up the patients for 30 days after ED admission to investigate any unintended consequences of our intervention (eg, treatment duration, length of stay, and costs) and to confirm that despite the characteristics of our study population, a trend toward the protective effect of ST intervention persisted. In addition, the study was performed in

a large teaching hospital that provided a structured ID consultant service, and its reproducibility could not be warranted in a facility without such a service. However, the effectiveness of this model, based on the early involvement of an ID specialist in the management of patients with SS/SS in the ED, could lead other healthcare organizations to implement collaborations with ID specialists.

To conclude, the early bedside intervention of ID specialists in the ED improves several issues related to sepsis management in the ED, including compliance with the SSC bundle, admission to the intensive care unit, and prompt administration of appropriate antimicrobial therapy, with a positive impact on patient outcome. The feasibility of such an approach in daily practice in different types of hospitals should be further investigated [Table 2].

Table 2. Univariate and Multivariate Cox Regression Analysis of Risk Factors for All-Cause 14-Day Mortality

	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Age	1.03 (1.01–1.04)	<.001	1.01 (1.00–1.03)	.05
Male sex	0.79 (0.56–1.11)	.18		
Charlson index	1.14 (1.06–1.22)	.001	1.01 (0.91–1.12)	.80
Prior antimicrobial exposure	0.89 (0.62–1.31)	.582		
Systemic inflammatory response syndrome (≥2 criteria)	0.89 (0.63–1.28)	.55		
Body temperature >38.3°C or <36°C	0.53 (0.35–0.80)	.003		
Heart rate >90 bpm	1.04 (0.73–1.48)	.80		
RR >20/min	1.06 (0.75–1.52)	.71		
White blood cell count >12c000/mmc or <4000/mmc	1.03 (0.71–1.49)	.85		
Quick sepsis-related organ failure assessment ≥2	2.09 (1.46–3.00)	<.001	1.68 (1.15–2.45)	.007
Altered mental status	2.01 (1.42–2.83)	<.001		
RR >20/min	1.06 (0.75–1.52)	.71		
Systolic blood pressure <100 mmHg	1.76 (1.25–2.48)	.001		
Serum lactate >2 mmol/L	2.37 (1.57–3.56)	<.001	2.13 (1.39–3.25)	<.001
Septic shock	2.01 (1.30–3.12)	.002	1.33 (0.83–2.14)	.23
Source of infection				
Lung	0.87 (0.62–1.24)	.45		
Urinary tract	0.55 (0.32–0.94)	.03		
Intraabdominal	0.63 (0.29–1.35)	.24		
Skin and soft tissue	0.52 (0.19–1.40)	.19		
Other	0.76 (0.31–1.87)	.56		
Unknown	2.53 (1.76–3.62)	<.001	2.07 (1.42–3.02)	<.001
Compliance with Surviving Sepsis Campaign bundle	0.75 (0.46–1.22)	.24		
Intensive care unit admission	0.94 (0.66–1.32)	.73		
Appropriate empiric antibiotic therapy	0.84 (0.60–1.19)	.35		
Post phase	0.67 (0.47–0.95)	.03	0.64 (0.43–0.94)	.026

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; CI, confidence interval; RR respiratory rate

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This study was funded by the Emilia Romagna Region, within the Research Program Regione-Università 2010–2012.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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