Outcomes in severe sepsis and patients with septic shock: Pathogen species and infection sites are not associated with mortality*

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Objectives: **We evaluated the respective influence of the causative pathogen and infection site on hospital mortality from severe sepsis related to community-, hospital-, and intensive care unit-acquired infections.**

Design: **We used a prospective observational cohort 10-yr database. We built a subdistribution hazards model with corrections for competing risks and adjustment for potential confounders including early appropriate antimicrobial therapy.**

Setting: **Twelve intensive care units.**

Patients: **We included 4,006 first episodes of acquisition-site-specific severe sepsis in 3,588 patients.**

Inteventions: **None.**

Measurements and Main Results: **We included 1562 community-acquired, 1432 hospital-acquired, and 1012 intensive care unit-acquired episodes of severe sepsis. After adjustment, we found no independent associations of the causative organism, multidrug resistance of the causative organism, infection site, or presence of bacteremia with mortality. Early appropriate antimicrobial therapy was consistently associated with better survival in the community-acquired (0.64 [0.51–0.8], $p = .0001$), hospital-acquired (0.72 [0.58–0.88], $p = .0011$), and intensive care unit-acquired (0.79 [0.64–0.97], $p = .0272$) groups.**

Conclusion: **The infectious process may not exert as strong a prognostic effect when severity, organ dysfunction and, above all, appropriateness of early antimicrobials are taken into account. Our findings emphasize the importance of developing valid recommendations for early antimicrobial therapy. (Crit Care Med 2011; 39:1886–1895)**

KEY WORDS: outcome; pathogens; place of acquisition; severe sepsis; site of infection

Severe sepsis, defined as sepsis associated with acute organ dysfunction, remains a leading cause of intensive care unit (ICU) admission, healthcare costs, workload, and death with mortality rates ranging from 30% to 50% despite advances in critical care management (1). Severe sepsis has a broad spectrum of clinical presentations. This clinical diversity may contribute to explain why the treatments evaluated in randomized controlled trials have not produced unequivocal evidence of efficacy.

Recognition that sepsis was a heterogeneous condition led to the development of the PIRO concept, in which P stands for predisposition to infection, I for the characteristics of the infection, R for the inflammatory response, and O for organ dysfunction. The goal of the PIRO concept was to better understand the differences and similarities among patients with sepsis. The underlying assumption was that the four components exerted independent effects on the likelihood of survival (2, 3). However, whether the characteristics of the infection independently affect the outcome remains debated. Conclusive evidence exists that early appropriate antimicrobial therapy improves survival in patients with sepsis (4, 5). In patients with septic shock, initiation of inappropriate antimicrobial therapy was associated with a fivefold decrease in survival (6). Thus, early appropriate antimicrobial therapy may be more effective than treatments directed specifically against the systemic inflammatory response.

A literature review on the contribution of the organism and infection site to the outcome of sepsis in 501 studies published over 30 yrs found that both parameters significantly influenced survival (7).

***See also p. 2001**.

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Furthermore, a significant interaction between the two parameters was noted. However, these overall results masked considerable variability across the included studies. Factors that may explain this variability include differences across ICUs and sample sizes; differences in case-mix related to patient selection for randomized controlled trials; inadequate adjustment for confounding factors; changes over time in the nature and susceptibility of the causative organisms; and changes in the treatments used. Many studies failed to adjust adequately for severity, organ dysfunction, and place of acquisition, which are associated with organism and infection site (1). More importantly, adequate adjustment for the appropriateness of initial antimicrobial therapy was often lacking.

The aim of this study was to evaluate the impact of the causative organism and infection site on hospital survival of patients with severe sepsis independently from the use of early appropriate antimicrobials and from the place of infection acquisition (community, hospital, or ICU).

METHODS

Data Source. We conducted a prospective observational study using data entered into a multicenter database (OUTCOMEREA) from November 1996 to August 2009. The database, fed by 12 French ICUs, contains data on admission features and diagnosis, daily disease severity, iatrogenic events, nosocomial infections, and vital status. Data for a random sample of at least 50 patients >16 yrs were consecutively entered into the database during a random period of time each year. Each participating ICU chose to perform sampling by taking either consecutive admissions to randomly selected ICU beds throughout the year or randomly consecutive admissions to all ICU beds over a single month.

Ethical Issues. According to French law, this study did not require patient consent, because it involved research on a database. The study was approved by the institutional review board of the Centres d'Investigation Rhône-Alpes-Auvergne.

Data Collection. Data were collected daily by senior physicians in the participating ICUs. For each patient, the data were entered into electronic case-report forms using VIGIREA and RHEA data-capture software (OUTCOMEREA, Paris, France), and all case-report forms were then entered into the OUTCOMEREA data warehouse. All codes and definitions were established before study initiation. The following information was recorded for each patient: age and sex, admission category (medical, scheduled surgery, or unscheduled surgery), origin (home, ward, or emergency room), and McCabe score. Severity of illness was evaluated on the first ICU day using the Simplified Acute Physiology Score and Sepsis-related organ Failure Assessment score. Knaus scale definitions were used to record pre-existing chronic organ failures, including respiratory, cardiac, hepatic, renal, and immune system failures. Relapse/recurrence was defined as a new episode of severe sepsis with the same micro-organism and the same infected organ. New episodes of severe sepsis involving different micro-organisms or different organs from the previous episode were classified as separate episodes (8).

Quality of the Database. The data-capture software automatically conducted multiple checks for internal consistency of most of the variables at entry in the database. Queries generated by these checks were resolved with the source ICU before incorporation of the new data into the database. At each participating ICU, data quality was controlled by having a senior physician from another participating ICU check a 2% random sample of the study data. A 1-day coding course is organized annually with the study investigators and contrast research organization monitors.

All prospectively recorded data describing the septic episodes and antimicrobial therapy were reviewed by two investigators (J.F.T. and C.A.) for face validity.

Study Population. Because diagnostic coding using the International Classification of Diseases classification has been found unreliable in the ICU (9), we used parameters collected prospectively by our data-capture software to select patients with severe sepsis, defined as systemic inflammatory response syndrome combined with an infectious episode and dysfunction of at least one organ. We excluded patients with treatment-limitation decisions taken before the diagnosis of severe sepsis (10). At least two of the following criteria were required for the diagnosis of systemic inflammatory response syndrome: core temperature ≥38°C or ≤36°C, heart rate ≥90 beats/min, respiratory rate ≥20 breaths/min, P_{CO_2} ≤32 mm Hg or use of mechanical ventilation, and peripheral leukocyte count ≥12,000/mm^3 or ≤4000/mm^3. Organ dysfunction was defined as follows: cardiovascular system failure was a need for vasoactive and/or inotropic drugs, and/or systolic blood pressure <90 mm Hg, and/or a drop in systolic blood pressure >40 mm Hg from baseline; renal dysfunction was urinary output ≤700 mL/day in a patient not previously undergoing hemodialysis for chronic renal failure; respiratory dysfunction was PaO_2 <70 mm Hg or mechanical ventilation or a PaO_2/FIO_2 ratio of ≤250 (or ≤200 in patients with pneumonia); thrombocytopenia was a platelet count <80,000/mm^3; and elevated plasma lactate was a value ≥3 mmol/L. Severe sepsis was defined as sepsis with at least one organ dysfunction as described previously, and septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation together with organ dysfunction; thus, patients receiving inotropic or vasoactive agents who had organ dysfunction but who were no longer hypotensive were classified as having septic shock. Lengths of ICU and hospital stays were determined starting at ICU admission.

The presence or absence of infection was documented according to the standard definitions developed by the Centers for Disease Control and Prevention and recently updated (11); in addition, quantitative cultures of specimens obtained by bronchoalveolar lavage, protected specimen brush, protected plugged catheter, or tracheal aspiration were required to diagnose ventilator-associated pneumonia (12). Community-acquired infection was defined as infection manifesting before or within 48 hrs after hospital admission. Hospital-acquired infection was infection manifesting at least 48 hrs after hospital admission but before ICU admission. ICU-acquired infection was diagnosed at least 48 hrs after ICU admission. We observed in our database that 20 species represented >90% of the infection, so we grouped the most important pathogens depending of the place of acquisition because the others were too rare to be specifically studied. Infection sites were categorized as follows: pneumonia, peritonitis, urinary tract infection, exacerbation of chronic obstructive pulmonary disease, catheter-related infection, primary bacteremia (excluding untreated *Staphylococcus epidermidis* bacteremia), miscellaneous sites (mediastinitis, prostatitis, osteomyelitis, and others), and multiple sites. Early appropriate antimicrobial therapy was defined as effectiveness on the causative agent of at least one of the empirically selected antimicrobials on the day of the diagnosis of an episode of severe sepsis. Effectiveness of antimicrobials was assessed based on the culture results and known susceptibility of the organism to the antimicrobials used and on antimicrobial susceptibility testing. For nonfermenting Gram-negative bacilli, aminoglycoside monotherapy was considered inappropriate (4). For undocumented infections, appropriateness of antimicrobial therapy was assessed based on published recommendations, depending on the infection site (13–16).

Statistical Analysis. The data were described as numbers (percentages) for categorical variables and medians (quartiles) for continuous variables. The Wald test p values reported in Tables 1, 2, and 3 were calculated using univariate subdistribution models. The primary evaluation criterion was death before hospital discharge. Survivors were censored after 60 days of follow-up.

Potential risk factors for death were entered in a Fine and Gray extension of a Cox model (17), in which ICU discharge was considered a competing event. The p values reported in Tables 1–3 were calculated using univariate subdistribution models. Infection sites and organisms were treated as classes that were predefined by the OUTCOMEREA expert committee based on data in the literature. Because

Table 1. Community-acquired severe sepsis (1562 episodes)

Variable	Survivors (n = 1178 episodes)	Decedents (n = 384 episodes)	p
Variables at intensive care unit admission			
Male gender	711 (60.4)	247 (64.3)	.23
Age	61 (47–72)	69 (54.5–79)	<.0001
Simplified Acute Physiology Score	42 (31–54)	61 (48–76)	<.0001
Sequential Organ Failure Assessment	6 (4–8)	9 (7–13)	<.0001
Admission category			.41
Medical	1044 (88.8)	331 (86.2)	
Emergency surgery	121 (10.3)	48 (12.5)	
Scheduled surgery	11 (0.9)	5 (1.3)	
McCabe score			<.0001
1	743 (63.2)	158 (41.1)	
2	372 (31.6)	166 (43.2)	
3	61 (5.2)	60 (15.6)	
Main symptom at admission			
Multiple organ failure	17 (1.4)	29 (7.6)	<.0001
Shock	337 (28.6)	147 (38.3)	.0002
Acute respiratory failure	433 (36.8)	116 (30.2)	.02
Exacerbation of chronic obstructive pulmonary disease	77 (6.5)	17 (4.4)	.11
Acute renal failure	46 (3.9)	12 (3.1)	.38
Coma	154 (13.1)	49 (12.8)	.77
Continuous monitoring	104 (8.8)	13 (3.4)	.0013
Comorbidities (Knaus definitions)			
Chronic respiratory failure	223 (18.9)	90 (23.4)	.07
Immunodeficiency	226 (19.2)	82 (21.4)	.25
Chronic heart failure	125 (10.6)	68 (17.7)	<.0001
Chronic hepatic failure	53 (4.5)	34 (8.9)	.002
Chronic renal failure	37 (3.1)	15 (3.9)	.39
Diabetes mellitus	135 (11.5)	51 (13.3)	.36
At least one chronic illness	519 (44.1)	220 (57.3)	<.0001
Septic shock	315 (26.7)	215 (56)	<.0001
Intensive care unit stay, days, median (interquartile range)	7 (4–13)	7 (3–14)	—
Hospital stay, days, median (interquartile range)	20 (11–34)	9 (3–18)	—
Treatment			
Corticosteroids	342 (29)	133 (34.6)	.02
Early appropriate antimicrobials	932 (79.1)	275 (71.6)	.002
Organisms			.24
Streptococcus pneumoniae	107 (9.1)	29 (7.6)	
Other Gram–positive	107 (9.1)	39 (10.2)	
Escherichia coli	87 (7.4)	35 (9.1)	
Other Gram–negative	123 (10.4)	55 (14.3)	
Other	40 (3.4)	10 (2.6)	
Undocumented	533 (45.2)	153 (39.8)	
Multiple organisms	181 (15.4)	63 (16.4)	
Multidrug–resistant bacteria	40 (3.4)	23 (6)	.04
Infection sites			.02
Pneumonia	458 (38.9)	138 (35.9)	
Intra–abdominal sites	99 (8.4)	36 (9.4)	
Urinary tract	89 (7.6)	42 (10.9)	
Other[a]	412 (35)	116 (30.2)	
Multiple sites	120 (10.2)	61 (15.9)	
Bacteremia	475 (40.3)	186 (48.5)	.004
Primary	187 (15.9)	59 (15.4)	
Secondary	288 (24.4)	127 (33.1)	

[a]Other: meningitidis, cellulitis, endocarditis, for instance.

Results were expressed as numbers (percentages) for categorical variables and as medians (quartiles) for continuous variables. *p* value: univariate subdistribution model (see statistical section). Sites of infection and organisms were handled as categories predefined by the OUTCOMEREA expert committee based on data in the literature (see statistical section). When there was more than one organism or site, the episode was classified only in the multiple organism or multiple site group. Episodes of bacteremia were classified as primary when no other site of infection was identified and as secondary when both the blood cultures and specimens from a clinically identified source grew the same micro-organism.

there was no reason *a priori* to consider that one infection site or micro-organism type was more severe than the others, infection site was handled as a multiple choice variable rather than as multiple dummy variables. However, before study initiation, we decided to test the role for multidrug-resistant pathogens and bacteremia.

Then, we used the multivariate subdistribution hazards model (17). Discharge alive from the ICU was handled as a competing event. A final model was built in five steps for each place of infection acquisition. First, we built a model with the severity variables that produced *p* values not >.20 in the univariate analyses (Simplified Acute Physiology Score, septic shock, age, and chronic illness). The Akaike criterion was used to select variables for this model (in particular, to choose between Simplified Acute Physiology Score on the one hand and Sepsis-related organ Failure Assessment score and age on the other). Second, we added the infection site and occurrence of positive blood cultures. Third, we added micro-organism type and multidrug resistance if present. Fourth, clinically relevant two-by-two interactions (pathogen–infection site) were tested. Fifth, we introduced therapeutic interventions (i.e., early appropriate antimicrobials and corticosteroids). Changing the order of the first three steps did not influence the final results. The subdistribution hazard ratios and 95% confidence intervals were calculated. *p* values < .05 were considered significant. Analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

Of the 11,992 patients in the OUTCOMEREA base, 3588 experienced 4425 episodes of severe sepsis. These 3588 patients were predominantly male (2250 [63%]) and had a median age of 65 yrs (range, 52–76 yrs) Simplified Acute Physiology Score score of 46 (range, 35–60), and Sepsis-related organ Failure Assessment score of 7 (range, 5–10). Crude hospital mortality was 30.4% (1090 patients). In each place-of-acquisition category, we studied only the first episode of severe sepsis, which left 4,006 episodes for the study, including 1,562 community-acquired, 1,432 hospital-acquired, and 1,012 ICU-acquired episodes (Fig. 1). The ICU and hospital stays were significantly longer in the ICU-acquired category than in the community-acquired category. Tables 1 through 3 report the main characteristics of the severe sepsis episodes. The main site of infection was the lung with pneumonia accounting for 40% to >50% of episodes in all three place-of-acquisition categories (Supplemental Table 1 [Supplemental Digital Content 1, http://

Table 2. Hospital-acquired severe sepsis (1432 episodes)

Variable	Survivors (n = 946)	Decedents (n = 486)	*p*
Variables at intensive care unit admission			
Male gender	572 (60.5)	314 (64.6)	.17
Age	65 (53–75)	71 (59–78)	<.0001
Simplified Acute Physiology Score	43 (33–53)	56 (44.5–73)	<.0001
Sequential Organ Failure Assessment	6 (4–9)	9 (6–12)	<.0001
Admission category			.18
Medical	636 (67.5)	341 (70.2)	
Emergency surgery	220 (23.4)	115 (23.7)	
Scheduled surgery	86 (9.1)	30 (6.2)	
McCabe score			<.0001
1	534 (56.7)	162 (33.3)	
2	348 (37)	248 (51)	
3	59 (6.3)	76 (15.6)	
Main symptom at admission			
Multiple organ failure	24 (2.5)	45 (9.3)	<.0001
Shock	346 (36.6)	201 (41.4)	.04
Acute respiratory failure	334 (35.3)	158 (32.5)	.17
Exacerbation of chronic obstructive pulmonary disease	27 (2.9)	10 (2.1)	.4
Acute renal failure	29 (3.1)	9 (1.9)	.18
Coma	68 (7.2)	35 (7.2)	.99
Continuous monitoring	83 (8.8)	25 (5.1)	.01
Comorbidities (Knaus definitions)			
Chronic respiratory failure	160 (16.9)	93 (19.1)	.34
Immunodeficiency	181 (19.1)	131 (27)	.0004
Chronic heart failure	99 (10.5)	83 (17.1)	.0002
Chronic hepatic failure	39 (4.1)	53 (10.9)	<.0001
Chronic renal failure	35 (3.7)	21 (4.3)	.52
Diabetes mellitus	114 (12.1)	64 (13.2)	.46
At least one chronic illness	424 (44.8)	308 (63.4)	.0001
Septic shock	247 (26.1)	233 (47.9)	.0001
Hospital stay before intensive care unit admission, days (interquartile range)	6 (2–13)	7 (3–16)	.02
Intensive care unit stay, days (interquartile range)	9 (5–17)	10 (5–18)	—
Hospital stay, days (interquartile range)	37 (23–63)	22 (13–38)	—
Treatments			
Corticosteroids	254 (26.8)	163 (33.5)	.0007
Early appropriate antimicrobials	742 (78.4)	346 (71.2)	.003
Organisms			.14
Staphylococcus aureus	62 (6.6)	40 (8.2)	
Other Gram–positive	72 (7.6)	35 (7.2)	
Nonfermentative GNB[a]	34 (3.4)	22 (4.5)	
Other Gram–negative	166 (17.5)	71 (14.6)	
Fungi only	14 (1.5)	7 (1.4)	
Other only	22 (2.3)	6 (1.2)	
Undocumented	413 (43.7)	192 (39.5)	
Multiple organisms	163 (17.2)	113 (23.3)	
Multidrug–resistant bacteria	75 (7.9)	62 (12.8)	.0004
Infection sites			.04
Pneumonia	314 (33.2)	167 (34.4)	
Intra–abdominal	150 (15.9)	68 (14)	
Urinary tract	72 (7.6)	22 (4.5)	
Other only[b]	287 (30.3)	142 (29.2)	
Multiple sites	123 (13)	87 (17.9)	
Bacteremia	349 (36.9)	214 (43)	.0002
Primary	144 (15.2)	76 (15.6)	
Secondary	205 (21.7)	138 (28.4)	

[a]Nonfermentative GNB, nonfermentative Gram-negative bacteria (*Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia*). *p* value: univariate subdistribution model; [b]other: meningitidis, cellulitis, endocarditis, for instance.

Results were expressed as numbers (percentages) for categorical variables and as medians (quartiles) for continuous variables. Sites of infection and organisms were handled as categories predefined by the OUTCOMEREA expert committee based on data in the literature (see statistical section). When there was more than one organism or site, the episode was classified only in the multiple organism or multiple site group. Episodes of bacteremia were classified as primary when no other site of infection was identified and as secondary when both the blood cultures and specimens from a clinically identified source grew the same micro-organism.

links.lww.com/CCM/A249]). The ICU-acquired group had significantly fewer episodes related to peritonitis and significantly more related to pneumonia, multiple infection sites, and intravascular catheters. Bacteremia was considerably more common in the community- and hospital-acquired categories than in the ICU-acquired category (Supplemental Table 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A249]). As expected, bacteremia (primary or associated with an infection site) was associated with higher mortality in the univariate analysis in all three place-of-acquisition categories.

We also analyzed two subgroups before and after 2005 (middle of the duration of the database) and found no time difference between these two periods (Supplemental Tables 2–4 [Supplemental Digital Content 1, http://links.lww.com/CCM/A249]).

Among causative organisms, aerobic Gram-negative bacteria were more common than aerobic Gram-positive bacteria. The contribution of aerobic Gram-negative bacteria and that of multiple bacteria increased from the community- to the hospital-acquired category and from the hospital- to the ICU-acquired category (Supplemental Table 1). Among causative organisms, the proportion with multidrug resistance was 4% in the community-acquired category, 9.6% in the hospital-acquired category, and 28.9% in the ICU-acquired category. Nonfermentative Gram-negative bacteria (*Pseudomonas* species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*), coagulase-negative *Staphylococcus*, and fungi were significantly more frequent in the ICU-acquired category than in the other two categories and were associated with higher mortality rates in the univariate analysis (Tables 1–3). Clinically suspected undocumented infections were less common in the ICU-acquired category (2.2%) than in the community-acquired (42.3%) or hospital-acquired (40.3%) categories and were not associated with mortality in the univariate analyses (see Supplemental Table 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A249]). If we took into account only severe sepsis with microbiologic documentation, the impact of antimicrobials remained similar for community-acquired and hospital-acquired severe sepsis (community-acquired: adjusted hazard ratio [95% confidence interval], 0.70 [0.51–0.95]; $p = .02$; hospital-acquired: adjusted hazard ratio [95% confidence interval], 0.85 [0.65–1.11]; $p = .25$), whereas it remains

Table 3. Intensive care unit-acquired severe sepsis (1012 episodes)

Variable	Survivors (n = 617)	Decedents (n = 395)	p
Variables at intensive care unit admission			
Male gender	400 (64.8)	278 (70.4)	.08
Age	63 (52–74)	70 (59–77)	<.0001
Simplified Acute Physiology Score	45 (35–57)	50 (39–65)	<.0001
Sequential Organ Failure Assessment	6 (4–8)	8 (6–11)	<.0001
Admission category			.75
Medical	425 (69)	276 (69.9)	
Emergency surgery	119 (19.3)	74 (18.7)	
Scheduled surgery	72 (11.7)	45 (11.4)	
McCabe score			<.0001
1	381 (61.9)	186 (47.1)	
2	211 (34.3)	175 (44.3)	
3	24 (3.9)	34 (8.6)	
Main symptom at admission			
Multiple organ failure	26 (4.2)	29 (7.3)	.02
Shock	163 (26.4)	122 (30.9)	.18
Acute respiratory failure	206 (33.4)	118 (29.9)	.21
Exacerbation of chronic obstructive pulmonary disease	22 (3.6)	12 (3)	.83
Acute renal failure	22 (3.6)	15 (3.8)	.90
Coma	91 (14.7)	50 (12.7)	.37
Continuous monitoring	47 (7.6)	29 (7.3)	.99
Comorbidities (Knaus definitions)			
Chronic respiratory failure	112 (18.2)	76 (19.2)	.62
Immunodeficiency	94 (15.2)	65 (16.5)	.39
Chronic heart failure	83 (13.5)	74 (18.7)	.03
Chronic hepatic failure	43 (7)	44 (11.1)	.02
Chronic renal failure	21 (3.4)	23 (5.8)	.01
Diabetes mellitus	85 (13.8)	47 (11.9)	.45
At least one chronic illness	278 (45.1)	225 (57)	<.0001
Time from admission to intensive care unit severe sepsis, days (interquartile range)	7 (4–11)	7 (4–11)	.06
Intensive care unit stay, days (interquartile range)	23 (14–40)	20 (13–31)	
Hospital stay, days (interquartile range)	49 (30–77)	28 (17–41)	
On the day of severe sepsis diagnosis			
Severity			
Septic shock	109 (17.7)	123 (31.1)	<.0001
Sequential Organ Failure Assessment	6 (4–8)	8 (6–11)	<.001
Sequential Organ Failure Assessment 2 days before diagnosis of severe sepsis	6 (4–8)	7 (5–10)	.001
Procedures			
Vasopressors	290 (47)	259 (65.6)	<.0001
Mechanical ventilation	518 (84)	356 (90.1)	.01
Arterial catheter	223 (36.1)	154 (39)	.21
Central catheter	349 (56.6)	242 (61.3)	.18
Swan–Ganz catheter	18 (2.9)	36 (9.1)	<.0001
At least one intravascular catheter	109 (17.7)	123 (31.1)	<.0001
Urinary tract catheter	579 (93.8)	362 (91.6)	.12
Treatments			
Corticosteroids	176 (28.5)	126 (31.9)	.23
Early appropriate antimicrobials	333 (54)	192 (48.6)	.18
Organisms			.1
Staphylococcus aureus	89 (14.4)	42 (10.6)	
Other Gram–positive	52 (8.4)	28 (7.1)	
Nonfermentative GNB[a]	85 (13.8)	61 (15.4)	
Other *Enterobacteriacae* species	52 (9.1)	40 (10.1)	
Other Gram–negative	69 (11.2)	41 (10.4)	
Fungi	33 (5.3)	33 (8.4)	
Other	45 (7.3)	15 (3.8)	
Multiple organisms	188 (30.5)	135 (34.2)	

strictly unchanged for ICU-acquired episodes.

After adjustment for severity, comorbidities, and early appropriate antimicrobials, we found no associations linking organism type, multidrug resistance, or infection site with mortality in any of the three place-of-acquisition categories. The early use of appropriate antimicrobials was associated with lower mortality in the community-acquired (0.64 [0.51–0.8], $p = .0001$), hospital-acquired (0.72 [0.58–0.88], $p = .0011$), and ICU-acquired (0.79 [0.64—0.97], $p = .0272$) categories (Tables 4–6). Overall this suggests similarity between documented infections vs. the other ones as long as we respect recommendation and adapt our choice on the ecology of our department. Of note, in none of the place-of-acquisition categories was clinically suspected undocumented infection or low-dose corticosteroid therapy associated with mortality. Furthermore, pooling all type of episodes (community-, hospital-, and ICU-acquired severe sepsis) did not influence our main results (Supplemental Table 5 [Supplemental Digital Content 1, http://links.lww.com/CCM/A249]).

DISCUSSION

We found that the characteristics of the infectious process were not independent predictors of inhospital mortality from severe sepsis. Thus, after adjustment for confounders including early appropriate antimicrobials, neither the infection site (with or without bacteremia) nor the causative organism (with or without multidrug resistance) was associated with mortality in any of the three place-of-acquisition groups (community, hospital, and ICU). This finding is in contrast to the results of studies that found an independent effect on mortality of each of the four PIRO components (predisposition, infection, response, and organ failure) (2, 3) but failed to adjust for early appropriate antimicrobials in addition to other confounders such as severity, comorbidities, and organ dysfunction (18).

Variations in case-mix, sepsis severity, organ dysfunction, specific infection sites studied and, above all, place of acquisition have been documented across ICUs and countries (1, 19–21). These factors may affect the distribution of infection sites and causative organisms, and they influence mortality. This variability in sepsis characteristics probably explains in large part the conflicting results in a review found among

Table 3.—*Continued*

Variable	Survivors (n = 617)	Decedents (n = 395)	*p*
Multidrug–resistant bacteria	163 (26.4)	129 (32.7)	.05
Infection sites			.50
Pneumonia	308 (49.9)	184 (46.6)	
Urinary tract	76 (12.3)	43 (10.9)	
Intra–abdominal sites	41 (6.6)	25 (6.3)	
Other[b]	144 (23.3)	103 (27.1)	
Multiple sites	48 (7.8)	36 (9.1)	
Bacteremia	105 (17)	103 (26.1)	.0001
Primary	35 (5.7)	33 (8.4)	
Secondary	70 (11.3)	70 (17.7)	

[a]Nonfermentative GNB, nonfermentative Gram-negative bacteria (*Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia*). *p* value: univariate subdistribution model; [b]other: meningitidis, cellulitis, endocarditis, for instance.

Results were expressed as numbers (percentages) for categorical variables and as medians (quartiles) for continuous variables. Sites of infection and organisms were handled as categories predefined by the OUTCOMEREA expert committee based on data in the literature (see statistical section). When there was more than one organism or site, the episode was classified only in the multiple organisms or multiple site groups. Episodes of bacteremia were classified as primary when no other site of infection was identified and as secondary when both the blood cultures and specimens from a clinically identified source grew the same micro-organism.

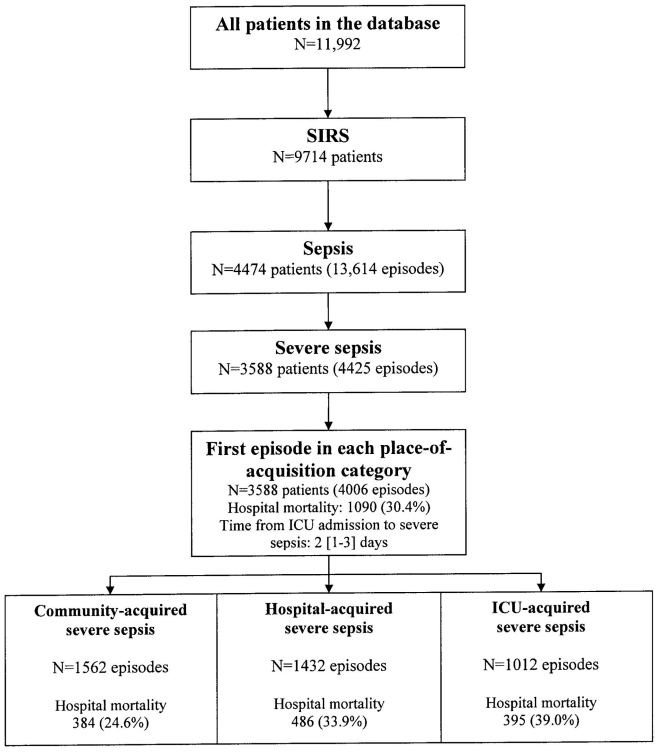

Figure 1. Flow diagram of the 3,588 patients with severe sepsis (4,006 episodes) who formed the basis for the study and who were taken from the 11,992 patients included in the OUTCOMEREA database. The first episode of severe sepsis was taken into account in each place-of-acquisition category (community, hospital, and intensive care unit [*ICU*]). Thus, some patients had more than one severe sepsis episodes included in the study (e.g., one community-acquired and one hospital- and/or ICU-acquired episode). Data are expressed as number (%). *SIRS*, systemic inflammatory response syndrome.

501 English-language studies of sepsis published >30 yrs (7). An important source of variation is place of acquisition (community, hospital, or ICU), which was associated with very different infection sites, causative pathogens, and outcomes in our study and in earlier work (1, 20). Failure to adjust for all confounding factors may also affect the results of studies of sepsis outcomes. Actually, crude mortality is often used as a marker for infection severity, which may be inappropriate, particularly in ICU patients, who are exposed to many other causes of death (22). We therefore conducted separate analyses of community-, hospital-, and ICU-acquired severe sepsis; and we adjusted for multiple potential confounders. The impact of early appropriate antimicrobials seemed to decrease from the community-acquired to the hospital-acquired category and from the hospital-acquired to the ICU-acquired category. One possible explanation to these differences is that, as the time goes by in the hospital or ICU, the underlying disease and comorbidities may make an increasingly large contribution to the risk of death.

The distributions of causative organisms and infection sites in our study were consistent with earlier reports (6, 19, 20, 23). Aerobic Gram-negative bacteria were more common than aerobic Gram-positive bacteria, and their prevalence increased from the community-acquired to the hospital-acquired group and from the hospital-acquired to the ICU-acquired group (Supplemental Table 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A249]). This finding may be related to the larger proportion of episodes related to multiple pathogens in the ICU group, as reported previously. In contrast to our findings, a survey of sepsis in the United States from 1979 to 2000 showed that Gram-positive bacteria became the predominant pathogens after 1987 (24) in keeping with other studies done in the early 2000s (2, 18, 21). However, recent studies, particularly those focusing on severe sepsis, showed a new trend toward a predominance of Gram-negative bacteria (19, 21, 25) consistent with our results. A decrease in *Staphylococcus aureus* has also been reported. In our study, the causative organism did not affect mortality, in keeping with recent data (17, 22, 26, 27) and in contradiction to earlier studies (7, 18).

Our findings do not challenge the fact that some strains are more virulent than others and that some infection sites are more likely than others to cause severe sepsis requiring ICU admission. However, when infected patients reach the same severity, the outcome is not affected any more by the initial virulence of the organism. Reasons for ICU referral include not only severe acute illness, but also severe underlying illnesses, a systemic response to infection, and organ dysfunction (Predisposition, Response, and Organ dysfunctions of the PIRO concept, respectively). Neither the infection site nor the micro-organism influences the mortality irrespective of the

Table 4. Influence of severity, infection site, and organism on inhospital mortality for the community-acquired episodes of severe sepsis

Variable	Subdistribution Hazard Ratio and Confidence Interval	*p* Value by Wald Chi-Square Test
Simplified Acute Physiology Score	1.05 (1.04–1.05)	<.0001
Septic shock	1.73 (1.39–2.16)	<.0001
At least one chronic illness	1.41 (1.13–1.74)	.002
Infection sites[a]		.39
Pneumonia	Reference	
Urinary tract	1.17 (0.78–1.77)	
Intra–abdominal sites	1.05 (0.71–1.55)	
Other	0.88 (0.67–1.16)	
Multiple sites	1.24 (0.89–1.71)	
Specific sites		
Bacteremia	1.11 (0.88–1.41)	.37
Organisms[a]		.55
Streptococcus pneumoniae	Reference	
Other Gram–positive	1.15 (0.7–1.88)	
Escherichia coli	0.95 (0.56–1.61)	
Other Gram–negative	1.09 (0.69–1.74)	
Other[b]	0.66 (0.3–1.47)	
Undocumented	1.12 (0.73–1.72)	
Multiple organisms	0.85 (0.54–1.34)	
Specific		
Multidrug–resistant bacteria	0.87 (0.54–1.40)	.56
Treatment		
Early appropriate antimicrobials	0.64 (0.51–0.80)	.0001
Corticosteroids	1.02 (0.82–1.28)	.85

[a]Reported organisms and infection sites are those in episodes with a single organism and single site; [b]anaerobic flora, other filamentous fungi, parasites, viruses.

Results were expressed as numbers (percentages) for categorical variables and as medians (quartiles) for continuous variables.

Table 5. Influence of severity, infection site, and organism on inhospital mortality for the hospital-acquired episodes of severe sepsis

Variable	Subdistribution Hazard Ratio and Confidence Interval	*p* Value by Wald Chi-Square Test
Simplified Acute Physiology Score	1.04 (1.03–1.04)	<.0001
Septic shock	1.45 (1.18–1.76)	.003
At least one chronic illness	1.62 (1.34–1.95)	<.0001
Infection sites[a]		.49
Urinary tract only	Reference	
Pneumonia only	1.41 (0.89–2.23)	
Intra-abdominal only	1.29 (0.79–2.12)	
Other only	1.32 (0.83–2.11)	
Multiple sites	1.51 (0.94–2.42)	
Specific sites		
Bacteremia	1.12 (0.91–1.37)	.29
Organisms[a]		.22
Other Gram-positive[b]	Reference	
Staphylococcus aureus	1.33 (0.83–2.12)	
Nonfermentative Gram-negative bacteria[c]	1.16 (0.67–2.00)	
Other Gram-negative	1.11 (0.73–1.67)	
Fungi	0.71 (0.3–1.69)	
Other[d]	0.75 (0.31–1.79)	
Undocumented	1.32 (0.91–1.91)	
Multiple organisms	1.44 (0.97–2.13)	
Specific		
Multiple drug-resistant bacteria	1.11 (0.82–1.52)	.49
Treatment		
Early appropriate antimicrobials	0.72 (0.58–0.88)	<.001
Corticosteroids	1.03 (0.84–1.25)	.79

[a]Reported organisms and infection sites are those in episodes with a single organism and single site; [b]*Streptococcus pneumoniae*, other streptococci, and coagulase-negative *Staphylococcus;* [c]*Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia;* [d]anaerobic flora, other filamentous fungi, parasites, viruses.

Results were expressed as numbers (percentages) for categorical variables and as medians (quartiles) for continuous variables.

place of acquisition. Conceivably, the favorable impact of the early appropriate antimicrobial therapy may be greater in patients with greater disease severity, for instance those with hemodynamic failure or bacteremia (6, 30, 31).

In our study, the lungs, abdomen, and urinary tract accounted for approximately 70% of cases of severe sepsis, in keeping with the literature (21). The presence of multiple infection sites was associated with mortality in the multivariate analyses (1, 20), but adjusting for early appropriate antimicrobials abolished this association. Bacteremia alone or in combination with focal infection has been consistently described as associated with greater disease severity (21, 32, 33). Thus, in a prospective cohort study, bacteremia was a feature in 17% of patients with sepsis, 25% of those with severe sepsis, and 69% of those with septic shock (31). We found that bacteremia was associated with mortality in the univariate analysis but not after adjusting for early appropriate antimicrobials. Furthermore, none of the other infection sites was associated with mortality in the adjusted analyses. Previously observed discrepancies may be related to comorbidities, age, and severity of severe sepsis (7, 18, 19, 24). Recent studies found higher mortality rates in patients with specific causative micro-organisms, particularly multidrug-resistant organisms such as *Pseudomonas aeruginosa* (Extended Study of Prevalence of Infection in Intensive Care II) (19) or fungi (33). However, the analyses were not adjusted for early appropriate antimicrobial therapy known to be associated with mortality (4, 19, 34). In keeping with our findings, several recent studies found that systemic inflammation and coagulation abnormalities were closely related with mortality but not with the nature of the causative organisms (17, 26–29). For instance, in patients with *S. aureus* ventilator-associated pneumonia, methicillin resistance had no impact on mortality after adjustment for confounders (35). The proportion of severe sepsis episodes related to fungi in our population was lower than in previous studies, for instance half that in the Extended Study of Prevalence of Infection in Intensive Care II studies (19). This difference may be related to differences in case-mix or to earlier appropriate use of antifungal drugs in high-risk patients in our study.

Clinically suspected undocumented infection may be difficult to confirm and does not allow a full assessment of the appropriateness of early antimicrobials. However,

Table 6. Influence of severity, infection site, and organism on inhospital mortality for the intensive care unit-acquired episodes of severe sepsis

Variable	Subdistribution Hazard Ratio and Confidence Interval	*p* Value by Wald Chi-Square Test
At admission		
Age	1.02 (1.01–1.03)	<.0001
At least one chronic illness	1.41 (1.15–1.72)	.001
On day 1 of severe sepsis		
Time in intensive care unit until severe sepsis onset	1.03 (1.01–1.05)	.002
Sequential Organ Failure Assessment	1.16 (1.12–1.19)	<.0001
Septic shock	1.28 (1.01–1.61)	.04
Infection sites[a]		.92
Urinary tract only	Reference	
Pneumonia only	1.01 (0.71–1.44)	
Intra-abdominal only	0.86 (0.51–1.43)	
Other only	0.91 (0.62–1.34)	
Multiple sites	0.98 (0.62–1.57)	
Specific sites		
Bacteremia	1.59 (1.22–2.06)	.0005
Organisms[a]		.42
Staphylococcus aureus	Reference	
Other Gram-positive[b]	0.95 (0.58–1.57)	
Nonfermentative Gram-negative bacteria[c]	1.28 (0.84–1.93)	
Other *Enterobacteriaceae*	1.31 (0.84–2.06)	
Other Gram-negative	1.28 (0.83–1.98)	
Fungi	1.25 (0.74–2.11)	
Other[d]	0.78 (0.43–1.42)	
Multiple organisms	1.33 (0.92–1.91)	
Specific		
Multidrug-resistant bacteria	0.98 (0.77–1.27)	.90
Treatment		
Early appropriate antimicrobials	0.79 (0.64–0.97)	.03

[a]Reported organisms and infection sites are those in episodes with a single organism and single site; [b]*Streptococcus pneumoniae*, other streptococci, and coagulase-negative *Staphylococcus;* [c]nonfermentative Gram-negative bacteria: *Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia;* [d]anaerobic flora, other filamentous fungi, parasites, viruses.

clinically suspected undocumented infections are very common among patients and must, therefore, be included in the analysis (21). In most sepsis episodes, the causative organism is unknown initially and the first antimicrobials must therefore be selected according to recommendations based on place of acquisition, local epidemiology of multidrug-resistant bacteria, patient colonization, and prior antimicrobials. In early studies, undocumented infection with severe sepsis was associated with higher mortality rates compared with documented infection (36). However, this finding was not replicated in recent studies, including ours. Thus, current recommendations may be effective in ensuring early appropriate antimicrobial therapy in patients with undocumented infection and severe sepsis.

We found that after adjustment for severity and organ dysfunction, and for early appropriate antimicrobials, the organism or resistance pattern did not affect mortality. Several studies found that early inappropriate antimicrobial therapy had little or no effect on mortality in patients with infection (37–40). However, the patients included in these studies had less severe infections with fewer hemodynamic disturbances, and the time to appropriate antimicrobial therapy was therefore probably less crucial compared with unselected patients with severe sepsis (37–41). In a study of septic shock, a shorter time from hypotension onset to appropriate antimicrobial therapy strongly predicted better survival (30).

Using the Simplified Acute Physiology Score III cohort, a study by Moreno et al (2) successfully built a variant of PIRO having three levels (Predisposition, Injury/Infection, and Response expressed as the Sepsis-related organ Failure Assessment score). This variant based only on objective criteria significantly predicted mortality in patients with sepsis. The respective role for each of the four PIRO components was assessed in a development cohort (Recombinant human protein C Worldwide Evaluation in Severe Sepsis [PROWESS] study) and validated in a large registry database (Prostate Cancer Genetic Research Study [PROGRESS]) (3). In both cohorts, infection (I component) was independently associated with mortality. However, the analyses were not adjusted for the severity of severe sepsis at diagnosis. Furthermore, infection was defined based on a variable combination of infection site and pathogen but failed to consider place of acquisition-community-, hospital-, and ICU-acquired severe sepsis as distinct entities or initial antimicrobial therapy. We only took into account the first episode of ICU-acquired severe sepsis. The occurrence of multiple episodes might have influenced our final results. However, <20% of patients underwent more than one episode of ICU-acquired severe sepsis and this hypothesis appeared unlikely.

A limitation of this study is the exact timing of the administration of the antibiotic is not available in the present study, particularly if it was an episode of hypotension.

In conclusion, after adjustment on confounders including early appropriate antimicrobials, the characteristics of the infectious process (site and causative organism) were not associated with mortality in patients with severe sepsis acquired in the community, hospital, or ICU. This finding highlights the need for careful attention to developing optimal international and local recommendations for selecting initial antimicrobials.

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