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ORIGINAL PAPER

The EPISEPSIS Study Group

EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units

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Abstract *Objective:* Ten years ago 8.4% of patients in French intensive care units (ICUs) were found to have severe sepsis or shock and 56% died in the hospital. As novel therapies for severe sepsis are emerging, updated epidemiological information is required. *Design and setting:* An inception cohort study conducted in 206 ICUs of randomly selected hospitals over a 2-week period in 2001, including all patients meeting criteria for clinically or microbiologically documented severe sepsis (with $\geq$1 organ dysfunction). *Measurements and results:* Among 3738 admissions, 546 (14.6%) patients experienced severe sepsis or shock, of which 30% were ICU-acquired. The median age of patients was 65 years, and 54.1% had at least one chronic organ system dysfunction. The median (range) Simplified Acute Physiology Score (SAPS II) and Sequential Organ Failure Assessment (SOFA) at onset of severe sepsis were 48 (2–129) and 9 (1–24), respectively. Mortality was 35% at 30 days; at 2 months the mortality rate was 41.9%, and 11.4% of patients remained hospitalized. The median (range) hospital stay was 25 (0–112) days in survivors and 7 (0–90) days in non-survivors. Chronic liver and heart failure, acute renal failure and shock, SAPS II at onset of severe sepsis and 24-h total SOFA scores were the independent risk factors most strongly associated with death. *Conclusions:* Although the attack rate of severe sepsis in French ICUs appears to have increased over the past decade, its associated mortality has decreased, suggesting improved management of patients. Severe sepsis incurs considerable resources use, and implementation of effective management strategies and continued research efforts are needed.

Keywords Sepsis · Cohort studies · Epidemiology · Prognosis · Organ failure

Introduction

Severe sepsis is a systemic inflammatory syndrome associated with infection and acute organ dysfunction, hypoperfusion or hypotension [1]. The attack rate of severe sepsis in intensive care units (ICUs), ranging between 5% and 19% [2, 3, 4, 5, 6, 7, 8, 9], appears to be increasing [3, 10]. Severe sepsis is the first cause of mortality in non-coronary ICUs [7, 10], with associated mortality rates ranging from 20 to 65% [2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14]. In the United States it is responsible for as many annual deaths as acute myocardial infarction [11].

The few available large epidemiological studies on severe sepsis are heterogeneous with regard to patients and ICU characteristics, and few provide a clear picture of the evolution of the condition over time [2, 3, 4, 5, 6, 7, 11, 12, 13]. Yet, such studies are important to increase our knowledge on the pathophysiology of severe sepsis, to improve the design of clinical trials and better assess the potential benefit of therapies. In 1993, we performed a large epidemiological study of patients with severe sepsis in French ICUs [4, 15]. Since then, the epidemiology of severe sepsis may have changed, particularly as a consequence of the increasing use of invasive procedures, and the growing number of aged and immunocompromised patients, both resulting in an increased risk of infection [3, 16]. On the other hand, technologies used in the ICU have evolved and progress has also occurred in the management of patients. As new adjuvant therapies for severe sepsis and shock are emerging [17, 18], updated epidemiological information is required.

To examine the current epidemiology of severe sepsis in French ICUs, in 2001 we performed a nationwide, prospective, multicenter survey evaluating the attack rate and characteristics of severe sepsis in a large and representative unselected patient population hospitalized in ICUs over two consecutive weeks. We also determined risk factors for death and investigated the relative contribution to hospital death of underlying conditions, acute physiologic alterations and organ failures.

Methods

The study was a national, prospective, multicenter survey of patients admitted to French ICUs over 2 weeks in 2001 (November 19 to December 2, 2001), before the licensing of drotrecogin alpha (activated) in France. All patients with severe sepsis present on admission or occurring during the ICU stay were included in the cohort and followed up until hospital discharge or 2 months after inclusion, whichever occurred first.

Intensive care unit registry

A registry of adult ICUs in French public and semi-private hospitals was generated by cross-checking the national hospital registry of the French central health agency (Direction Générale de la Santé) and the two major associations of intensive care physicians (Société de Réanimation de Langue Française and Société Française d'Anesthésie et de Réanimation). Nearly 500 ICUs were identified in 12 regions of comparable population, of which 300 (60%) ICUs, stratified by region, were randomly selected and invited to participate in the study.

Data collection

Severe sepsis or shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Conference criteria (i.e. suspected or documented infection associated with at least one organ dysfunction) [1]. For patients included in the cohort, we recorded their demographic characteristics, ICU admission characteristics, the presence of co-morbidities and overall severity of pre-existing underlying disease, if any, according to McCabe's classification [19]. The severity of acute illness was assessed using the Simplified Acute Physiology Score (SAPS II) [20] at ICU admission and onset of severe sepsis, and the Sequential Organ Failure Assessment (SOFA) [21] score within 24 hours of onset of severe sepsis (see the ESM for details). For the purpose of analysis, individual organ dysfunction was defined as a score higher than 0 and organ failure as a score of 3 or more; septic shock was considered present when the cardiovascular dysfunction score was 3 or more. We also recorded the type of documentation of infection (clinically or microbiologically documented), its mode of acquisition and source, and category of microorganism involved.

Data evaluation and quality control

Data were collected in each ICU by experienced physicians using standardized forms and entered in a computer program. The program included reliability checks based on ranges for physiological and biological data, and logical checks for inconsistencies and missing data. Members of the EPISEPSIS steering committee reviewed, prior to data entry, all forms from patients in whom the diagnosis of severe sepsis was equivocal. In addition, data accuracy was checked against original charts for all case report forms from a random sample of 5% participating units.

Statistical analysis

Data analysis and calculations were performed with SAS statistical software (version 8.02, SAS Institute, Cary, NC). A number of variables were assessed as potential risk factors for death in patients with severe sepsis with use of the chi-square or the Mann-Whitney test. Variables associated with death at a p level less than 0.15 were entered in a Cox's multivariable stepwise logistic regression model, with time to hospital death as the dependent variable. Variables remaining significantly associated with death at the p =0.05 or less level in the multivariable analyses were retained as independent risk factors in the final models and their odds ratio (OR) estimates with 95% confidence intervals were calculated. Variables entered in the multivariable analyses included: age, sex, co-morbidity, the McCabe class, the SAPS II score at ICU admission and at onset of severe sepsis, type of documentation, site and origin of acquisition of infection, and SOFA score at 24 h after the onset of the severe sepsis (total score as well as score for each organ system). Two multivariable analyses were performed, one including all variables selected at a p less than 0.15 level in bivariate analyses, and one omitting the McCabe classification and the total SOFA score, to examine the individual role of each specific chronic or acute organ dysfunction.

Results

Participating intensive care units

Among the 300 ICUs invited, 213 (71.0%) agreed to participate in the study. However, seven ICUs were excluded from the analysis due to missing forms, leaving 206 (68.7%) ICUs analyzed. During the quality control procedure, 8.5% of all severe sepsis forms were checked, and missing or incorrect data represented 6.2%. The ICUs were in university and/or regional hospitals (n=95; 46.1%), general hospitals (n=97; 47.1%) or semi-private hospitals (n=14; 6.8%). A majority (77.2%) of ICUs were in large (>400 beds) hospitals. There were 125 (60.7%) mixed medico-surgical ICUs, 49 (23.8%) surgical and 32 (15.5%) medical ICUs. Nineteen units (9.2%) had 6 beds or less, 145 (70.4%) had between 7 and 15 beds, and 42 (20.4%) had more than 15 beds.

Occurrence of severe sepsis

During the 2-week study period, 3738 patients were screened for severe sepsis and 621 (16.6%) were identified as having a first episode of clinically suspected severe sepsis. Clinically or microbiologically documented infection was recorded in 546 (87.9%) of them, giving an overall rate of "documented " severe sepsis of 14.6% (546/3738). Severe sepsis was identified on ICU admission in 382 (70.0%) patients. In the remaining 164 (30.0%) patients, severe sepsis occurred 3 or more (median, 5) days after ICU admission and was classified as ICU-acquired.

The attack rate of severe sepsis was higher in university and/or regional (307/2,009 ICU admissions; 15.3%) and general hospitals (214/1435; 14.9%) than in semi-private hospitals (25/294; 8.5%, p=0.008), and in ICUs housed in large (>400 beds) than in smaller ($\leq$400 beds) hospitals (461/3,000; 15.4% versus 76/655; 11.6%, respectively; p=0.016). However, the number of beds per ICU did not influence the rate of severe sepsis. The attack rate of severe sepsis was higher in patients admitted to a medical (131/760; 17.2%) or medico-surgical (294/1,959; 15.0%) ICU than in those admitted to a surgical ICU (121/1,019; 11.9%; p=0.005).

Extrapolating our findings to France (59.6 million population), after adjustment for the type of hospital and ICU, the yearly attack rate of severe sepsis in French ICUs was estimated at 0.95 episodes per 1000 inhabitants and the total annual number of episodes in ICUs at 56,540.

Table 1 Clinical characteristics of 546 patients with documented severe sepsis

Clinical characteristic	
Age, median (range), years	65 (16–93)
Men/women, *n*	365/181
Occurrence of sepsis, *n* (%)	
At ICU admission	427 (78.2)
ICU-acquired	119 (21.8)
Time between ICU admission and severe sepsis, days (range)*	5 (1–314)
Admission category, *n* (%)[a]	
Medical	311 (57.4)
Unscheduled surgery	162 (29.9)
Scheduled surgery	40 (7.4)
Trauma	29 (5.4)
Transfer from, *n* (%)[b]	
Emergency room	197 (36.3)
Medical ward	151 (27.8)
Surgical ward	109 (20.1)
Operating/recovery room	61 (11.2)
Another ICU	25 (4.6)
Co-morbidities, *n* (%)	
Immunodepression	124 (22.7)
Metastatic cancer	41 (7.5)
Hematological malignancy	29 (5.3)
Acquired immunodeficiency syndrome	10 (1.8)
Other causes	44 (8.1)
Chronic respiratory insufficiency	91 (16.7)
Chronic heart failure	71 (13.0)
Type I diabetes	39 (7.1)
Chronic liver insufficiency	34 (6.2)
Chronic renal insufficiency	24 (4.4)
Number of co-morbidities, *n* (%)	
None	251 (46.0)
One	221 (40.5)
Two or more	74 (13.6)
Severity of underlying disease, *n* (%)[c]	
No underlying disease	146 (27.0)
Non-fatal	180 (33.3)
Ultimately fatal	162 (29.9)
Rapidly fatal	53 (9.8)
SAPS II score at ICU admission, median (range)[d]	47 (2–124)
SAPS II score at onset of severe sepsis, median (range)	48 (2–124)
Total SOFA score 24 h after onset of severe sepsis, median (range)[d]	9 (1–24)

* In patients with ICU-acquired sepsis (n=164)
[a] n=542; [b]n=543; [c]n=541; [d]n=544

Characteristics of patients with severe sepsis

There were twice as many men as women with severe sepsis; the median age of patients was 65 years (Table 1). The majority of patients had a medical admission (57.4%); more than half (54.1%) had at least one co-morbidity, notably immunodepression (22.7%). A rapidly or ultimately fatal underlying disease was recorded in 9.8% and 29.9% of patients, respectively. The median (range) SAPS II and SOFA scores recorded within 24 h of the onset of severe sepsis were 48 (2–129) and 9 (1–24), respectively. Respiratory and cardiovascular failure (i.e. shock) occurred within 24 h of admission in 56.9% and 55.8% of patients, respectively (Table 2); neurological

Table 2 Organ dysfunction/failures recorded along time in 546 patients with severe sepsis

Day of study	24 h	72 h	7 days	14 days
Discharged alive, total[a]	0	10	73	165
Deaths, total	3	73	111	151
Missing data	2	9	24	32
Number of patients remaining analyzed on study day	541	454	338	198
Organ dysfunction/failure, *n* (%)[b]				
Respiratory				
Dysfunction	502 (92.8)	398 (87.0)	286 (84.6)	166 (83.8)
Failure	308 (56.9)	192 (42.3)	119 (35.2)	53 (26.8)
Cardiovascular				
Dysfunction	420 (77.6)	288 (63.4)	146 (43.2)	68 (34.3)
Failure	302 (55.8)	213 (46.9)	107 (31.6)	42 (21.2)
Neurological				
Dysfunction	443 (81.9)	329 (72.4)	240 (71)	142 (71.7)
Failure	162 (29.9)	105 (23.1)	65 (19.2)	31 (15.6)
Renal				
Dysfunction	371 (68.6)	254 (55.9)	156 (46.2)	85 (42.9)
Failure	113 (20.9)	72 (15.9)	41 (12.1)	28 (14.1)
Hematological				
Dysfunction	247 (45.7)	201 (44.3)	102 (30.2)	35 (17.7)
Failure	63 (11.6)	63 (13.9)	29 (8.6)	12 (6.1)
Hepatic				
Dysfunction	252 (46.6)	195 (43.0)	123 (36.4)	67 (33.8)
Failure	34 (6.3)	34 (7.5)	29 (8.6)	14 (7.0)
Mean SOFA score (SD)	9.7 (4.2)	8.3 (4.5)	6.4 (4.4)	5.3 (3.9)

[a] The cumulative number of patients being discharged or having died from onset of sepsis to the day of study is shown in rows.
[b] Percentages are given relative to the actual number of patients evaluated on each day. For each organ system, dysfunction is defined as a SOFA score greater than 0 and failure as a score of 3 or more.

(29.9%), renal (20.9%), hematological (11.6%) and liver (6.3%) failure were less common. Infection was identified clinically or microbiologically in 37.9% and 62.1% of patients, respectively. The characteristics of infection are reported in the electronic supplementary material (see ESM, Table S1)

Outcome of patients

The outcome of patients with severe sepsis is shown in Table 3 and Fig. 1. The 30-day mortality rate was 35% (Fig. 1); at 2 months after inclusion, 46.7% of the patients had been discharged alive, 41.9% had died in the hospital and 11.4% were still hospitalized. The outcome of patients was comparable regardless of whether sepsis was acquired in hospital or in the ICU. Mortality was highest in patients admitted for medical-related reasons (44.4%) and lowest in those admitted for trauma (31.0%). Similarly, mortality was highest (53.0%) in patients transferred from hospital wards. The overall median (range) length of ICU stay from onset of severe sepsis was 11 (0–90) days; in survivors, the median duration of ICU and hospital stay was, respectively, 12 (range: 0–80) and 25 (0–112) days. The median duration from the diagnosis of severe sepsis to death was 7 (0–90) days.

Risk factors for death in patients with severe sepsis

In bivariate analyses, increasing age ($p<0.0001$), congestive heart failure ($p=0.0002$) and chronic liver insufficiency ($p=0.002$) were significantly associated with death (Table 4). Both severity of acute illness scores (SAPS II and total SOFA score) at onset of severe sepsis were associated with death ($p<0.0001$). Dysfunction of each of the six organ systems included in the SOFA score were also strongly associated with mortality, with a p value ranging from less than 0.0001 (renal, cardiac or neurological failure) to less than 0.001 (respiratory or hematological failure) and 0.013 (hepatic failure). In contrast, the type of documentation, mode of acquisition or source of infection did not influence mortality ($p=0.7$ and $p=0.9$, respectively).

Multivariable analyses confirmed that the three scores assessing the severity of acute or chronic illness were independent risk factors for death (Table 5, model 1). In addition to the acute physiology scores [20, 21], the McCabe classification [19] remained strongly associated with the risk of hospital death. As compared with having no underlying disease, an ultimately or rapidly fatal underlying disease was associated with a significantly ($p<0.001$) higher risk of death (OR 2.79 [95 CI 1.6–4.87] and 2.65 [95% CI, 1.19–5.88], respectively). When omitting the McCabe classification from the analysis and substituting each of the acute organ failures (defined

Table 3 Admission characteristics and two-month outcome of 546 patients with severe sepsis

	Hospital survivors	Still in hospital at 2 months	Hospital death	*p* value[a]
Number (%) patients	255 (46.7)	62 (11.4)	229 (41.9)	
Onset of severe sepsis				0.47
- at admission to ICU	206 (48.2)	43 (10.1)	178 (41.7)	
- acquired in ICU	49 (41.2)	19 (16.0)	51 (42.9)	
ICU stay from diagnosis of severe sepsis, median (range), days	12 (0–80)	15 (1–78)	7 (0–90)	0.035
Admission category[a]				0.52
- Medical	141 (45.3)	32 (10.3)	138 (44.4)	
- Unscheduled surgery	75 (46.3)	20 (12.3)	67 (41.4)	
- Scheduled surgery	21 (52.5)	4 (10.0)	15 (37.5)	
- Trauma	16 (55.2)	4 (13.8)	9 (31.0)	
Transfer from[b]				0.051
- Emergency room	99 (50.3)	20 (10.2)	78 (39.6)	
- Medicine	57 (37.7)	14 (9.3)	80 (53.0)	
- Surgery	55 (50.5)	17 (15.6)	37 (33.9)	
- Operating/recovery room	30 (49.2)	6 (9.8)	25 (41.0)	
- Other ICU	11 (44.0)	5 (20.0)	9 (36.0)	

Data are shown as number (%) of patients, unless otherwise stated.
[a] *p* value for comparison between hospital survivors and non-survivors
[a] *n*=542; [b]*n*=543

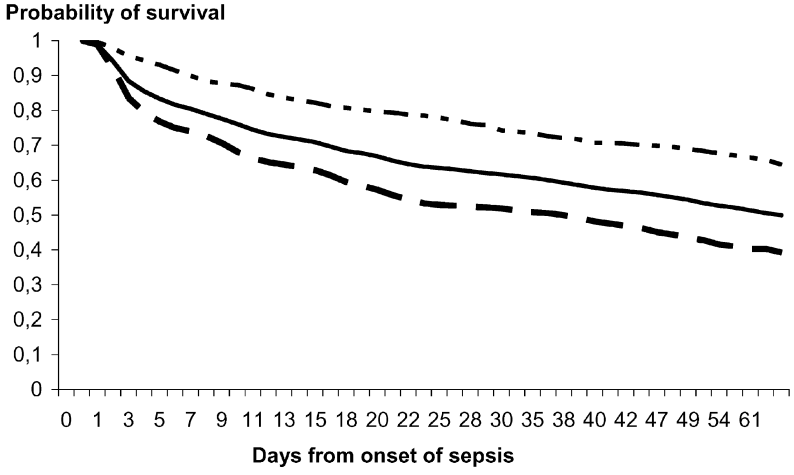

Fig. 1 Probability of death along time after onset of severe sepsis (whole cohort, *solid line*) and segregated for patients with (*lower broken line*) or without (*upper broken line*) cardiovascular failure (i.e. septic shock)

as a SOFA score of 3 or more) for the total SOFA score (Table 5, model 2), chronic liver and heart failure emerged as independent risk factors for death, as well as acute renal failure and cardiovascular failure (i.e. shock), while the SAPS II score at 24 h of severe sepsis was retained in the model.

Finally, we examined separately the relative contribution of each acute organ failure to hospital mortality, independently of other risk factors. In this analysis, the acute organ failures most strongly associated with outcome were, in decreasing order of importance, renal failure (OR 3.1; 95% CI 1.98–4.94, $p<0.0001$), shock (OR 2.4; 1.65–3.55, $p<0.0001$), coma (OR 2.1; 1.44–3.22, $p=0.0002$), and respiratory failure (OR 1.5; 1.03–2.23, $p=0.03$). The two remaining organ failures included in the SOFA score (i.e. respiratory and hematological failures) were not retained in the analysis, after adjustment for other organ failures. Examining outcome of patients as a function of the evolution of organ failures within the first 72 h of onset of severe sepsis (Table 2), we found that the persistence or development of coma (OR 2.56 and 5.7, respectively), renal failure (OR 2.9 and 4.1), liver failure (OR 2.9 and 3.2) and shock (OR 2.4 and 2.6) were most strongly associated with outcome.

Discussion

Compared with our previous studies performed in 1993, which used the same definition of severe sepsis [4, 15], data from this study suggest a 75% increase in the attack rate of severe sepsis in ICU patients over the past decade

Table 4 Outcome of 546 patients with severe sepsis, according to patients' clinical characteristics (bivariate analysis)

	Death	Survival	*p* value[a]
Age, median (range), years	70 (18–93)	61 (16–92)	<0.001
Gender			0.99
- Male, *n* (%)	153 (41.9)	212 (58.1)	
- Female, *n* (%)	76 (42.0)	105 (58.0)	
Immunocompromised status, *n* (%)	58 (49.2)	60 (50.8)	0.07
Chronic respiratory disease, *n* (%)	46 (50.5)	45 (49.5)	0.07
Congestive heart failure, *n* (%)	44 (62.0)	27 (38.0)	0.002
Type I diabetes	19 (48.7)	20 (51.3)	0.37
Chronic liver insufficiency	23 (67.6)	11 (32.4)	0.002
Chronic renal insufficiency	14 (58.3)	10 (41.7)	0.10
McCabe's classification, *n* (%)			<0.001
No underlying disease affecting prognosis	39 (26.7)	107 (73.3)	
Non-fatal disease	66 (36.7)	114 (63.3)	
Ultimately fatal (<5 years)	88 (54.3)	74 (45.7)	
Rapidly fatal (<1 year)	34 (64.2)	19 (35.8)	
SAPS II score at onset of severe sepsis, median (range)	60 (21–121)	42 (2–124)	<0.0001
Total SOFA score 24 h after the onset of severe sepsis, median (range)	12 (1–24)	7 (1–19)	<0.0001

[a] Mann-Whitney test for continuous variables and chi-square test for dichotomous variables

Table 5 Risk factors for hospital death in 546 patients with severe sepsis (multivariable analyses)

	Odds ratio estimates	95% confidence interval	*p* value
Model 1[a]			
McCabe's risk class			0.0003
No underlying disease affecting prognosis	1	-	-
Non-fatal disease	1.20	0.69–2.09	
Ultimately fatal (<5 years)	2.79	1.60–4.87	
Rapidly fatal (<1 year)	2.65	1.19–5.88	
Total SOFA score 24 h after the onset of severe sepsis (per point)	1.16	1.09–1.24	<0.0001
SAPS II score at onset of severe sepsis (per point)	1.04	1.02–1.05	<0.0001
Model 2[b]			
Chronic liver failure	3.5	1.47–8.34	0.005
Chronic heart failure	2.27	1.26–4.08	0.0006
Cardiovascular failure	1.62	1.06–2.48	0.025
Acute renal failure	1.69	1.01–2.82	0.043
SAPS II score at onset of severe sepsis (per point)	1.05	1.04–1.06	<0.0001

[a] Model 1 included all variables found associated to hospital death in bivariate analyses, i.e. age, gender, McCabe's class, co-morbidities, SAPS II score at ICU admission and at onset of severe sepsis, characteristics of infection (site and mode of acquisition), SOFA score at 24 h of onset of severe sepsis (total score and individual score for each of the neurological, respiratory, cardiovascular, renal, hematological and liver organ failures).
[b] Variables included in the second model: same as in model 1, after excluding McCabe's classification and total SOFA score

(from 8.4% and 6.3% for clinically or microbiologically documented severe sepsis to 14.6% and 9.0%). This increase is comparable to the 8.7% annual increase in sepsis rate found in a recent analysis of the discharge diagnoses from 1979 to 2000 in a large sample of US hospitals [10]. Improved care of the elderly and of immunocompromised patients, plus the widespread use of invasive devices, have all probably contributed to this increasing rate [3, 16]. As shown previously [4], the rate of severe sepsis differed according to the hospital size, which may reflect the fact that patients at higher risk are preferentially hospitalized in large hospitals.

The 42% hospital mortality rate recorded in this study is similar to that reported recently from the European Sepsis Database (40%) [2, 14], and is substantially lower than the 59% corresponding rate recorded in our previous study [4]. These results tend to confirm that mortality associated with severe sepsis has decreased over the past decade, as also recently reported from a large investigation in the USA [10]. A recent review of studies published from 1958 to 1997 also found a reduction in mortality

from septic shock [22]. The mean age of patients was comparable in our two studies. Although a larger proportion of patients (67%) in this study were male, gender did not influence outcome, a finding supported by another study specifically addressing this issue [8]. The apparently lower mortality rate we recorded in 2001 is due in part to a lower severity of disease, as reflected by the mean (± SD) SAPS II score at onset of sepsis (56±18 in the 1993 study versus 51±20 in this study). However, this difference in severity score would account for an expected decrease in mortality of only 11%; the decreasing mortality rate in the past decade is also likely related to increased awareness and a better detection of the syndrome leading to earlier intervention [23], and to an improved overall therapeutic management of patients.

An important finding from our study is that almost 12% of patients remained hospitalized at 2 months after sepsis. Their median length of ICU stay was 11 days overall and the mean (SD) and median (range) hospital stay in survivors were 16.2 (18) and 25 (0–112) days, respectively. Other studies have also documented a protracted hospital stay in a substantial proportion of patients with severe sepsis [4, 7, 11, 14]. For example, in our previous survey, 16% of patients were still in hospital 30 days after the occurrence of sepsis [4]. In the PROWESS trial, more than 40% of the patients were still in hospital at 28 days [18]. Therefore, follow-up in sepsis trials should be extended longer, up to 3 months, to capture the overall pattern of hospital outcome of patients [24].

Infection was documented in nearly 90% of the cases with suspected severe sepsis, similarly to our previous survey [4]. However, the rate of microbiologically documented infection was about 10% lower (from 70.5% to 62.1%), possibly reflecting a larger and earlier use of empiric antimicrobial therapy prior to sampling. Our results also confirm that gram-positive organisms currently account for a majority of the infections [10, 22]. The prevalence of nosocomial infection appeared comparable to our previous data (51.6% versus 49.5% in the present study [4]), and pulmonary infection was confirmed as the most important source of severe sepsis in the ICU. However, the characteristics of infection had no significant impact on prognosis [4].

Since the recent licensing of activated (recombinant) protein C, a novel therapy for sepsis, has been associated to severity of disease [18, 25], it is important to determine predictors of outcome and the relative contribution of various indices used for grading severity to help characterize patients who might benefit from such therapy. We therefore examined a number of potential predictors of death, including severity scores and organ failures. We confirmed the prognostic value of the SAPS II score, a robust general severity index predicting the risk of death in critically ill patients [20]. As previously noted by others [26, 27], this score had a greater prognostic value when measured at the onset of severe sepsis than when measured at ICU admission, highlighting the importance of the timing of assessment of severity scores in sepsis.

The SOFA score, which characterizes the degree of dysfunction/failure by organ system, was primarily designed to describe morbidity [21, 28]. However, higher values of this organ dysfunction score remained as a strong independent risk factor of mortality, even after adjustment for the SAPS II score. A similar finding was recently described in critically ill patients [29]. Therefore, both a general severity index and an organ dysfunction score should be measured at inclusion of patients in sepsis studies, and they can be used for stratification of patients and for adjustment when assessing outcome.

We also examined the relative contribution of each organ dysfunction to outcome in a separate analysis omitting the global SOFA score (Table 5). Whereas respiratory failure was the most common organ failure recorded in our cohort, this variable was not a major predictor of death, possibly reflecting improved management of mechanical ventilation in this population. Conversely, renal failure had the largest influence on outcome, followed by cardiovascular failure (i.e. shock) and coma. The combination of shock and renal failure thus appears associated with the highest risk of mortality in patients with severe sepsis. Of note, liver failure, which usually develops at a later stage in severe sepsis, was associated with outcome when organ failures were assessed at 72 h.

Despite the large influence on outcome of patients of the general severity scores, other variables reflecting underlying conditions retained prognostic significance after adjustment for these scores. As previously emphasized, the McCabe classification was strongly associated with the risk of mortality [4, 30]. However, this index may have poor inter-observer reproducibility and has not been widely used in sepsis trials, despite its simplicity [29]. Among major co-morbidities, chronic liver insufficiency and congestive heart failure appear as the most strongly associated with the risk of death, since these two variables were selected after omitting the global severity of underlying disease classification from the analysis (Table 5). Similar findings were reported from the analysis of the European Sepsis Database [14]. Therefore, when performing stratification or risk adjustments in outcome analyses of sepsis studies, such as performed in the PROWESS trial [18, 31], investigators may be willing to substitute these two variables for the McCabe classification.

These results also confirm the sub-optimal performance of general, non-disease-specific severity scores in a selected patient population, thus providing a rationale for customizing prognostic models in sepsis [12, 32]. In addition to the above-mentioned variables, other factors not measured in our study may have some influence on outcome in patients with severe sepsis and help refine

prognostication. Cytokine levels or other markers of inflammation may be listed among these, as suggested by a recent expert panel [33].

We believe that our large survey gives a valid and representative picture of the global pattern of severe sepsis in France in 2001. The duration of enrolment was short, to allow for the participation of a high number of units and a large and representative sample of French hospitals of various affiliation. There was no selection of patients, no patient was lost to follow-up and the latter extended up to 2 months in an attempt to assess the outcome fully. A recent estimate from UK reported an attack rate of severe sepsis on ICU admission of 51/100,000 population [34]; given that 78% of our patients had severe sepsis on ICU admission, the corresponding figure for France derived from this study (74/100,000) appears consistent with the UK estimate.

Severe sepsis is a frequent and often fatal disorder and its attack rate has increased over the past 10 years in French ICUs, affecting nearly 15% of ICU patients. Although mortality appears to have decreased in the past decade, it is still high and considerable morbidity remains associated with this syndrome, as demonstrated by the impact on outcome of organ failures and the protracted hospital stay of a large proportion of patients. Since the incidence of sepsis is expected to increase further as the population ages [10, 11], implementation of effective management strategies and continued research efforts to improve the outcome of such patients are needed.

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References

1. Bone RC, Balk RA, Cerra FB, Dellinger EP, Fein AM, Knaus WA, Schein RM, Sibbald WJ, the ACCP/SCCM Consensus Conference Committee (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101:1656–1662
2. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulmé R, Lepage E, Le Gall JR (2002) Epidemiology of sepsis and infection in ICU patients from an international multicenter cohort study. Intensive Care Med 28:108–121 (Erratum p 526)
3. Angus DC, Wax RS (2001) Epidemiology of sepsis: an update. Crit Care Med 29:S109–S116
4. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Régnier B (1995) Incidence, risk factors and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. JAMA 274:968–974
5. Edbrooke DL, Hibbert CL, Kingsley JM, Smith S, Bright NM, Quinn JM (1999) The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care unit. Crit Care Med 27:1760–1767
6. Salvo I, de Cian W, Musico M, Langer M, Piadena R, Wolfler A, Montant C, Magni E, the Sepsis Study Group (1995) The Italian SEPSIS study: Preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. Intensive Care Med 21:S244–S249
7. Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, Parsonnet J, Panzer R, Orav EJ, Snydman DR, Black E, Schwartz JS et al. (1997) Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA 277:234–240
8. Wichmann MW, Inthorn D, Andress HJ, Schildberg FW (2000) Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. Intensive Care Med 26:167–172
9. Brun-Buisson C (2000) The epidemiology of the systemic inflammatory response. Intensive Care Med 26:S64–S74
10. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554
11. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med 29:1303–1310
12. Le Gall JR, Lemeshow S, Leleu G, Klar J, Huillard J, Rué M, Teres D, Artigas A, The ICU Scoring Group (1995) Customized probability models for early severe sepsis in adult intensive care patients. JAMA 273:644–650
13. Rangel-Frausto MS, Pittet D, Costigan MD, Hwang T, Davis CS, Wenzel RP (1995) The natural history of the systemic inflammatory response syndrome. JAMA 273:117–123
14. Alberti C, Brun-Buisson C, Goodman SV, Guidici D, Granton J, Moreno R, Smithies M, Thomas O, Artigas A, Le Gall JR (2003) Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. Am J Respir Crit Care Med 168:77–84
15. Brun-Buisson C, Doyon F, Carlet J (1996) Bacteremia and severe sepsis in adults: a multicenter prospective survey in ICUs and wards of 24 hospitals. Am J Respir Crit Care Med 154:617–624
16. Safdar N, Maki DG (2002) The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile and Candida. Ann Intern Med 136:834–844
17. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
18. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut J-F, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
19. Kreger BE, Craven DE, Carling P, McCabe WR (1980) Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. Am J Med 68:332–343

20. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European-North American multicenter study. JAMA 270:2957–2963
21. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26:1793–1800
22. Friedman G, Silva E, Vincent JL (1998) Has the mortality of septic shock changed with time? Crit Care Med 26:2078–2086
23. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
24. Cohen J, Guyatt G, Bernard GR, Calandra T, Cook DJ, Elbourne D, Marshall J, Nunn A, Opal SM (2001) New strategies for clinical trials in patients with sepsis and septic shock. Crit Care Med 29:880–886
25. Dhainaut JF, Laterre PF, Janes JM, Bernard GR, Artigas A, Bakker J, Riess H, Basson BR, Charpentier J, Utterback BG, Vincent JL (2003) Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Med 29:894–903
26. Pittet D, Thiévent B, Wenzel RP, Li N, Auckenthaler R, Suter PM, Thievent B (1996) Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients. Am J Respir Crit Care Med 153:684–693
27. Russell JA, Singer J, Bernard GR, Wheeler A, Fulkerson WJ, Hudson L, Schein R, Summer W, Wright P, Walley KR (2000) Changing pattern of organ dysfunction in early human sepsis is related to mortality. Crit Care Med 28:3405–3411
28. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758
29. Timsit JF, Fosse JP, Troche G, De Lassence A, Alberti C, Garrouste-Org, Azoulay E, Chevret S, Moine P, Cohen Y (2001) Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h. Intensive Care Med 27:1012–1021
30. Gross PA, Stein MR, van Antwerpen C, DeMauro PJ, Boscamp JR, Hess W, Wallenstein S (1991) Comparison of severity of illness indicators in an intensive care unit. Arch Intern Med 151:2201–2205
31. Ely EW, Laterre PF, Angus DC, Helterbrand JD, Levy H, Dhainaut JF, Vincent JL, Macias WL, Bernard GR (2003) Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med 31:12–19
32. Knaus WA, Harrel FE, Fisher CJ, Wagner DP, Opal SM, Sadoff JC, Draper EA, Walawander CA, Conboy K, Grasela TH (1993) The clinical evaluation of new drugs for sepsis: a prospective study design based on survival analysis. JAMA 270:1233–1241
33. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 31:1250–1256
34. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K (2003) Epidemiology of severe sepsis occurring in the first 24 h in intensive care units in England, Wales and Northern Ireland. Crit Care Med 31:2332–2338