Journal of Critical Care 53 (2019) 46–52

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Trends in the incidence and mortality of patients with community-acquired septic shock 2003–2016

Jordi Valles [a,*], Dionisia Fontanals [b], Joan Carles Oliva [c], Melcior Martínez [a], Ana Navas [a], Jaume Mesquida [a], Guillem Gruartmoner [a], Candelaria de Haro [a], Jaume Mestre [a], Consuelo Guía [a], Andrey Rodriguez [a], Eva Torrents [a], Cristina Espinal [a], Ana Ochagavía [a], Emili Diaz [a]

[a] *Critical Care Department, Hospital Universitari Parc Taulí, Sabadell, Spain*
[b] *Microbiology Department, Hospital Universitari Parc Taulí, Sabadell, Spain*
[c] *Fundació Parc Taulí, Hospital Universitari Parc Taulí, Sabadell, Spain*

ARTICLE INFO

Keywords:
Community-acquired infections
Sepsis
Septic shock
ICU
Outcome
Source control

ABSTRACT

Purpose: To evaluate the incidence and mortality of adult patients with community-acquired septic shock (CASS) and the influence of source control (SC) and other risk factors on the outcome.
Material and methods: The study included patients with CASS admitted to the ICU at a university hospital (2003–2016). Multivariate analyses were performed to identify risk factors of ICU mortality.
Results: A total of 625 patients were included. The incidence showed an average annual increase of 4.9% and the mortality an average annual decrease of 1.4%. The patients who required SC showed a lower mortality (20.4%) than patients who did not require SC (31.3%) ($p = 0.002$). However, the evolution in mortality was different: Mortality decreased in patients who did not require SC (from 56.3% to 20%; $p = 0.02$), but did not differ in those who required SC (from 21.4% to 27.6%; $p = 0.43$). In the multivariate analysis, severity at admission, age, alcoholism, cirrhosis, ARDS, neutropenia and thrombocytopenia were associated with worse outcome, whereas appropriate antibiotic treatment and adequate SC were independently associated with better survival.
Conclusions: The incidence of CASS increased and the ICU mortality decreased during the study period. The mortality was mainly due to a decrease in mortality in infections not requiring SC.

© 2019 Published by Elsevier Inc.

1. Introduction

Sepsis is a major health public problem; septic shock is the most severe form of sepsis and accounts for much of its morbidity and mortality. Despite major technological advances, septic shock related mortality remains high, ranging from 20% to 50% [1-3]. Recent reports show an increase in the incidence of septic shock and a decrease in its associated mortality; however, changes in diagnostic coding may have overestimated these trends [4-7].

Recently, the third international consensus definitions for sepsis and septic shock (Sepsis-3) defined septic shock as a subset of sepsis associated with a greater risk of mortality than sepsis alone in which patients have serum lactate >2 mmol/L despite adequate fluid resuscitation and require vasopressor therapy to maintain mean arterial blood pressure ≥ 65 mmHg [8].

We used clinical data to evaluate the local epidemiology of patients with septic shock according to Sepsis-3 admitted to the intensive care unit (ICU) during a 14-year period. Our main objective was to estimate annual incidence rates and mortality trends for patients admitted with community-acquired septic shock (CASS). Secondary objectives included characterizing patients with CASS and analyze the influence of source control (SC) on the outcome and identifying other risk factors associated with poor prognosis.

2. Material and methods

2.1. Study population

This retrospective observational cohort study included consecutive adult (>18 years old) patients admitted to the ICU at a university hospital in Spain (January 1, 2003 through December 31, 2016) with CASS. Trained research physicians used a standardized, piloted data form to collect data and select patients from a prospectively registered database of all patients admitted to the ICU with community-acquired infection

---

Abbreviations: CASS, Community-acquired septic shock; SC, Source control; AKI, Acute kidney injury; ARDS, Acute respiratory distress syndrome; AIDS, Acquired immunodeficiency syndrome; COPD, Chronic obstructive pulmonary disease; RRT, Renal replacement therapy; IQR, Interquartile range.

[*] Corresponding author at: Critical Care Department, Hospital Universitari Parc Taulí, Pac Tauli s/n 082018, Sabadell, Spain.
E-mail address: jvalles@tauli.cat (J. Valles).

https://doi.org/10.1016/j.jcrc.2019.05.025
0883-9441/© 2019 Published by Elsevier Inc.

during the study period. The database was performed by only two investigators (JV and ED) with experience in infectious diseases and with homogeneous diagnostic criteria during the study period.

All had a first-time diagnosis of septic shock within 48 h of ICU admission and had no other obvious cause of shock. Patients with healthcare-acquired infections were excluded. The hospital's ethics committee approved the study and waived the need for informed consent due to its observational nature (Ethics Committee Corporació Sanitaria Universitaria Parc Taulí, 2018/610).

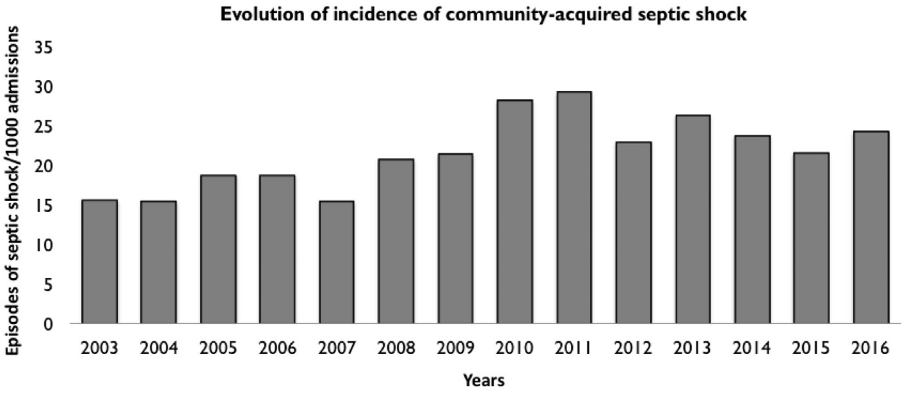
2.2. Data abstraction and definitions

Septic shock was defined as sepsis with hypotension requiring vasopressor therapy to maintain mean arterial blood pressure ≥ 65 mmHg for ≥48 h, SOFA score > 2 at ICU admission, and serum lactate >2 mmol/L despite adequate fluid resuscitation [8].

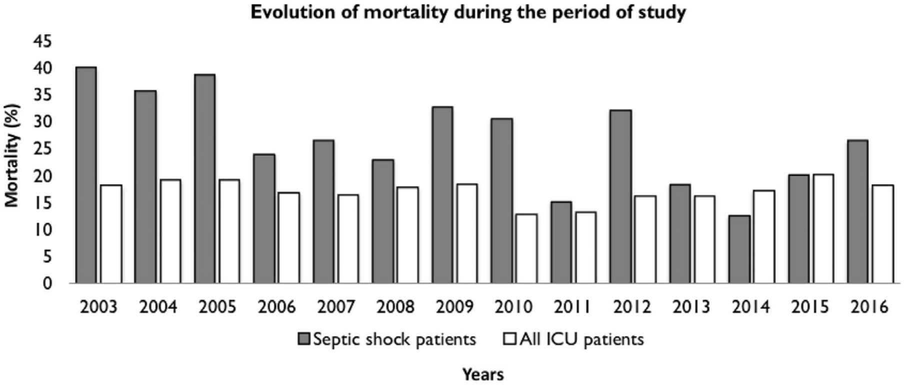
Variables included year of admission for septic shock, demographics (age, sex), and baseline comorbidities (AIDS, cancer, cirrhosis, heart failure (NY-II), chronic obstructive pulmonary disease (COPD), chronic renal failure requiring dialysis, diabetes mellitus, and alcohol abuse), diagnosed according to criteria reported elsewhere [9]. Patients were considered immunocompromised if they had severe neutropenia (absolute neutrophil count <500/microL), immunodeficiency secondary to cytotoxic drugs, or steroid treatment (20 mg prednisolone or equivalent/day ≥2 weeks). Pathogens were considered potential causes of septic shock if isolated or identified from the local site and/or blood cultures within 48 h of septic shock onset and were classified as culture-negative, gram-positive bacteria, gram-negative bacteria, anaerobes, fungi or other. We also recorded the presence of bacteremia and fungemia. Initial empirical antibiotic treatment was considered appropriate if ≥1 antibiotic administered within 24 h of first contact with the patient matched the in vitro susceptibility of the pathogen considered the likely cause of infection. The appropriateness of antibiotic therapy was not analyzed for episodes of septic shock with negative cultures. Treatment decisions, including antibiotic prescriptions, were taken by attending physicians following protocols based on local adapted guidelines.

Sources of infection were classified based on clinical diagnosis and/or isolation of pathogens as follows: respiratory infection, intraabdominal infection (peritonitis, abscess, small-bowel obstruction, spontaneous bacterial peritonitis, *Clostridium difficile*–associated colitis, organ perforation, enterocolitis or diverticulitis, ischemic bowel, pancreatitis, or other), biliary infection (cholecystitis or cholangitis), genitourinary infection (pyelonephritis, obstructive uropathy–associated urinary tract infection, or gynecologic infections), skin and soft-tissue infection (cellulitis, abscess, or necrotizing fasciitis), or other.

In episodes where SC was necessary, attending physicians decided what type of control was necessary (percutaneous/endoscopic or surgical). We recorded classified patients into those who received SC < 12 h or > 12 h of diagnosis of CASS. Source control was considered adequate if patients improved after intervention (disappearance of fever, normalization of white blood counts, improvement of acute phase reactants,



Increase in incidence in septic shock patients: mean annual increase, 4.9% (95% CI: 1.8%–8.0%); p=0.005 for linear trend



Decrease in mortality in septic shock patients: mean annual decrease, 1.4% (95% CI: 0.4–2.3); p=0.009 for linear trend.

Fig. 1. Evolution of incidence and mortality of septic shock during the study period.

and decrease in doses of vasopressors required) and required no new intervention on the same focus during the ICU stay. In cases where these variables could not be reviewed, the effectiveness of SC was not evaluated.

We recorded complications of septic shock measured at or after ICU admission that could be related to the natural history and/or management of septic shock: acute kidney injury (AKI), thrombocytopenia, acute respiratory distress syndrome (ARDS), and need for mechanical ventilation or renal replacement therapy (RRT). AKI was defined as an increase in serum creatinine ≥0.3 mg/dL within 48 h or 1.5 to 1.9 times baseline creatinine [10] and thrombocytopenia as <150,000 platelets/μl [11]. ARDS was defined as $PaO_2/FiO_2 < 300$ mmHg with bilateral thoracic infiltrates, excluding heart failure [12].

Severity at admission included SOFA [11] and APACHE II [13] scores. Patients were followed up until death or hospital discharge. The primary outcome variables were survival to ICU discharge and to hospital discharge.

2.3. Statistical analysis

We used chi-square or Fisher's exact tests to compare categorical variables and Student's *t*-test or the Mann-Whitney U–test to compare continuous variables, as appropriate. ICU and hospital length of stay was expressed as median and interquartile range (IQR). The IQR is the difference between the first and third quartiles. Medians were compared using the Mann-Whitney test. All variables significant in the univariate analyses were included in the logistic regression models. All tests were two-tailed, and $P < 0.05$ was considered significant. SPSS version 23.0 for Windows (SPSS, Armonk, NY: IBM Corp.) was used for all analyses.

3. Results

Of 29,624 patients admitted to the ICU during the study period, 625 (mean age, 65.5 ± 14.4 years; male sex, 372 (59.5%); mean APACHE II at admission, 20.5 ± 6.3; mean SOFA at admission, 9.1 ± 2.5) met the criteria for CASS, representing a mean annual incidence rate of 21.09 episodes/1000 admissions, increasing from 15.6 episodes/1000 admissions in 2003 to 24.3 episodes/1000 admissions in 2016 (mean annual increase, 4.9%; 95% CI: 1.8%–8.0%; $p = 0.005$ for linear trend) (Fig. 1).

Table 1 reports patients' characteristics. The most common comorbidities were diabetes (29.1%), cancer (20%), and COPD (15.2%). Infection was documented by positive cultures in 576 (92.2%) patients. Blood cultures were positive in 328 (52.5%). Gram-negative microorganisms accounted for 41.6%, and gram-positive microorganisms for 33.1%. The most frequent gram-positive microorganisms were *Streptococcus pneumoniae* (28.5% with bacteremia), *Staphylococcus aureus* (62.5% with bacteremia), and *Streptococcus pyogenes* (36% with bacteremia). The most frequent gram-negative microorganisms were *Escherichia coli* (78.2% with bacteremia), *Klebsiella pneumoniae* (84.2% with bacteremia), and *Pseudomonas aeruginosa* (71.4% with bacteremia). Empiric antibiotic treatment was appropriate in 544 (94.4%) of the 576 patients with positive cultures.

The most common source of CASS was respiratory infection (27%), followed by genitourinary infection (22.0%) and intraabdominal infection (20%). SC was required in 322 (51.5%) patients (64.2% surgical procedures and 35.8% percutaneous/endoscopic procedures). SC interventions were performed within 12 h of septic shock onset in 72% of patients, of which 62.3% required surgical control and 37.7% percutaneous/endoscopic control ($p = 0.03$), and were adequate in 87.4% of the 254 cases where its effectiveness could be evaluated. Tables 2 and 3 show the characteristics of patients with SC vs. patients who did not require SC and among patients with adequate SC vs. patients in whom the SC was not effective. Patients who did not require SC showed more previous comorbidities, and greater incidence of respiratory infections and ARDS than patients who required SC.

The most common complication of CASS was AKI (555 (88.8%) patients, 132 (23.7%) of whom required RRT, followed by thrombocytopenia (390 (62.5%) patients) and ARDS (142 (22.8%) patients); 410 (65.7%) patients required invasive mechanical ventilation.

The mean mortality associated with CASS during the study period was 25.8% in the ICU and 29.6% in the hospital. Septic shock associated ICU mortality decreased from 40% in 2003 to 26.5% in 2016 (average annual decline, 1.4% (95% CI:0.4–2.3); $p = 0.009$ for linear trend), while the overall mortality in our ICU did not change significantly during the study period. (Fig. 1). Multivariate linear regression to assess the relationship between changes in mortality over time (as percentages) and year, APACHE II, and SOFA showed that changes in ICU mortality in patients with CASS were independent of APACHE II and SOFA scores.

Mortality differed depending on the origin of sepsis; mortality secondary to intraabdominal infections was 34.4%, skin and soft-tissue infections 31.6%, respiratory infections 29.6%, biliary infections 17.5%, and genitourinary infections 7.9%.

Mortality was lower in patients who required SC (20.8% vs. 31.3% in those who did not require SC; $p = 0.002$) (Table 2). Among patients who required SC, mortality was lower in those undergoing

Table 1
Characteristics of patients.

All patients	N:625
Age, mean (±SD), years	65.6 (14.4)
APACHE II, mean (±SD)	20.5 (6.3)
SOFA score, mean (±SD)	9.1 (2.5)
Sex, male (%)	372 (59.5)
Comorbidities, n (%)	
HIV/AIDS	24 (3.8)
Diabetes	182 (29.1)
Chronic obstructive pulmonary disease	95 (15.2)
Alcohol	64 (10.2)
Cirrhosis	47 (7.5)
Cancer	125 (20)
Chronic kidney disease (Dialysis)	14 (2.2)
Cardiac failure (NY-II)	71 (11.4)
Neutropenia	22 (3.5)
Corticosteroid therapy	50 (8)
Chemotherapy	78(12.5)
Bacteremia, n (%)	328 (52.5)
Pathogens, n (%)	
Gram-negative	260 (41.6)
Gram-positive	207 (33.1)
Anaerobes	17 (2.7)
Fungi	4 (0.6)
Others[a]	3 (0.5)
Polymicrobial	85 (13.6)
Culture negative	49 (7.8)
Appropriate empiric antibiotic therapy, n (%)[b]	544 (94.4)
Source, n (%)	
Respiratory	169 (27.0)
Genitourinary	138 (22.1)
Intrabdominal	125 (20.0)
Biliary	80 (12.8)
Skin and soft tissue	80 (12.8)
Others[c]	33 (5.3)
Source control, n (%)	322 (51.5)
Type of source control, n (%)[d]	
Non-invasive (percutaneous or endoscopic)	115 (35.8)
Invasive (surgical)	207 (64.2)
Time of source control, n (%)[d]	
<12 h	232 (72.0)
>12 h	90 (28.0)
Adequate source control, n (%)[e]	222 (87.4)
ICU LOS (days), median (IQR)	8 (10)
Hospital LOS (days), median (IQR)	19 (21)
Mortality, n (%)	161 (25.8)

[a] Influenza, *Mycoplasma pneumonia, Pneumocystis jirovecii.*

[b] Over 576 patients with positive culture.

[c] Bone and join infection, endocarditis, meningitis, ears, nose and throat (ENT), and unknown origin.

[d] Over 322 patients who need source control.

[e] Over 254 patients who source control could be evaluated.

Table 2
Characteristics of patients with and without source control.

Variable, n (%)	Patients with source control (n: 322), n (%)	Patients with no source control (n: 303), n (%)	p
Age, mean (±SD), years	67.10 (14.16)	64.14 (14.5)	0.007
APACHE II, mean (±SD)	19.12 (5.28)	22.16 (7.00)	<0.001
SOFA, mean (±SD)	8.64 (2.47)	9.71 (2.56)	<0.001
Sex			
Male	179 (55.6)	200 (66.0)	0.002
Female	143 (44.4)	103 (34.0)	
Comorbidities			
Diabetes	83 (25.7)	99 (32.6)	0.344
Cancer	67 (20.8)	58 (19.1)	0.589
COPD	39 (12.1)	56 (18.5)	0.028
Alcoholism	23 (7.1)	41 (13.5)	0.009
Dialysis	8 (2.5)	6 (1.2)	0.666
Cirrhosis	14 (4.3)	33 (10.9)	0.002
Chronic cardiac failure	37 (11.5)	34 (11.2)	0.904
Corticosteroids	18 (5.6)	32 (10.6)	0.023
Immunosuppression	27 (8.4)	51 (16.8)	0.001
Neutropenia	6 (1.2)	16 (5.3)	0.021
HIV	2 (0.6)	22 (7.3)	<0.001
Complications			
Acute kidney failure	286 (88.8)	268 (88.4)	0.798
Renal replacement therapy	64 (19.9)	68 (22.4)	0.444
Thrombocytopenia	205 (63.7)	184 (60.7)	0.450
Mechanical ventilation	211 (65.5)	199 (65.7)	0.945
ARDS	31 (9.6)	111 (36.6)	<0.001
Bacteremia	169 (52.4)	159 (52.4)	0.966
Microbiology			<0.001
Gram-positive	69 (21.4)	138 (45.5)	
Gram-negative	159 (49.3)	101 (33.3)	
Anaerobes	10 (3.1)	7 (2.3)	
Fungi	4 1.2)	0 (0)	
Others[a]	0 (0)	3 (1)	
Polymicrobial	66 (20.5)	19 (6.3)	
Negative culture	14 (4.3)	35 (11.5)	
Source			<0.001
Respiratory	1 (0.3)	168 (55.4)	
Abdominal	101 (31.4)	24 (7.9)	
Genitourinary	80 (24.5)	58 (19.1)	
Skin and soft tissue	65 (20.2)	15 (4.9)	
Biliary	74 (22.3)	6 (1.2)	
Others[b]	1 (0.3)	32 (10.6)	
Appropriate antibiotic treatment[c]	289 (93.8)	255 (95.1)	0.485
ICU mortality	67 (20.8)	95 (31.3)	0.002

[a] *Influenza, Mycoplasma pneumoniae, Pneumocystis jirovecii.*
[b] Arthritis, endocarditis, ORL, SNC, unknown origin.
[c] Over 576 patients with positive culture (308 with source control and 268 with not source control).

percutaneous/endoscopic interventions (10.4% vs. 26.5% in those undergoing surgical interventions; $p < 0.001$). In 222 (87.4%) of the 254 cases where its effectiveness could be evaluated, ICU mortality was higher in patients with inadequate SC (84.4% vs. 10.8% in patients with adequate SC; $p < 0.001$) (Table 3).

During the study period, mortality decreased from 56.3% in 2003 to 20% in 2016 ($p = 0.02$) among patients who did not require SC but did not differ in those requiring SC (21.4% in 2003 to 27.6% in 2016; $p = 0.43$) (Fig. 2). There was a nonsignificant trend toward increased mortality with delayed SC (25.5% for SC >12 h vs. 19% for SC <12 h; $p = 0.19$).

Table 4 reports variables significantly associated with ICU mortality in the univariate analyses. Variables independently associated with worse prognosis in the multivariate analysis for ICU mortality adjusted for age, comorbidities, and severity at ICU admission were APACHE II, cirrhosis, ARDS, age, and thrombocytopenia (Table 5). Appropriate antibiotic treatment was independently associated with better survival.

We repeat a multivariate analysis in the group of patients without SC, and the APACHE II, ARDS and cirrhosis were the variables independently associated with a poor prognosis. The multivariate analysis in the group who needed a SC showed that mechanical ventilation, APACHE II and alcoholism were the variables associated a poor prognosis in those patients. Instead, appropriate antibiotic therapy and adequate source control were independently associated with a better survival (Table 5).

4. Discussion

This study using Sepsis-3 definitions from 2003 to 2016 found an increase in the incidence of CASS in patients admitted to the ICU. Our findings that the incidence rate of septic shock increased an average of 4.9% per year are identical to those of a recent study in 27 US academic medical centers during a ten-year period [7]. The increased incidence of sepsis is often attributed to better surveillance to recognize septic patients, aging of the population, and increased use of invasive procedures and immunosuppressive therapies [14,15]. Despite the increase in incidence found in our study, the reported annual incidence is lower than in other

Table 3
Characteristics of patients with evaluable source control (n:254).

Variable	Patients with adequate source control (n:222), n (%)	Patients with no adequate source control (n:32), n (%)	p
Age, mean (±SD), years	66.9 (14.46)	69.53 (12.12)	0.460
APACHE II, mean (±SD)	18.34 (5.14)	21.66 (5.11)	<0.001
SOFA, mean (±SD)	8.40 (2.27)	9.53 (2.38)	0.015
Sex			
Male	117 (52.7)	15 (46.9)	0.537
Female	105 (47.3)	17 (53.1)	
Comorbidities			
Diabetes	70 (31.5)	6 (18.7)	0.140
Cancer	47 (21.2)	7 (21.9)	0.928
COPD	30 (13.5)	4 (12.5)	0.875
Alcoholism	17 (7.65)	2 (6.25)	0.777
Dialysis	5 (2.25)	0 (0)	0.391
Cirrhosis	7 (3.15)	2 (6.25)	0.379
Chronic cardiac failure	26 (11.7)	5 (15.6)	0.527
Corticosteroids	15 (6.75)	0 (0)	0.130
Immunosuppression	19 (8.55)	3 (9.37)	0.878
Neutropenia	4 (1.80)	1 (3.12)	0.614
HIV	2 (0.90)	0 (0)	0.590
Complications			
Acute kidney failure	200 (90.0)	29 (90.6)	0.924
Renal replacement therapy	43 (19.4)	11 (34.3)	0.052
Thrombocytopenia	139 (62.6)	22 (68.7)	0.500
Mechanical ventilation	140 (63.1)	32 (100)	<0.001
ARDS	16 (7.2)	6 (18.7)	0.030
Bacteremia	117 (52.7)	16 (50.0)	0.775
Microbiology			0.013
Grampositive	45 (20.3)	11 (34.3)	
Gramnegative	114 (51.3)	9 (28.1)	
Anaerobes	6 (2.7)	4 (12.5)	
Polymicrobial	42 (18.9)	7 (21.9)	
Others[a]	0 (0)	0 (0)	
Negative culture	13 (5.8)	1 (3.1)	
Source			<0.001
Abdominal	65 (29.3)	13 (40.6)	
Genitourinary	57 (25.7)	3 (9.4)	
Skin and soft tissue	38 (17.1)	16 (50.0)	
Biliary	61 (27.5)	0 (0)	
Respiratory[b]	1 (0.45)	0 (0)	
Early source control (⟨12*h*)	165 (74.3)	23 (71.8)	
Type source control			<0.001
Invasive (surgical)	134 (60.4)	30 (93.7)	
Non-invasive (percutaneous or endoscopic)	88 (39.6)	2 (6.3)	
Appropriate antibiotic treatment[c]	197 (94.2)	30 (96.7)	0.564
ICU mortality	24 (10.8)	27 (84.4%	<0.001

[a] *Influenza, Mycoplasma pneumoniae, Pneumocystis jirovecii.*
[b] One case of empyema.
[c] Over 240 patients with positive culture.

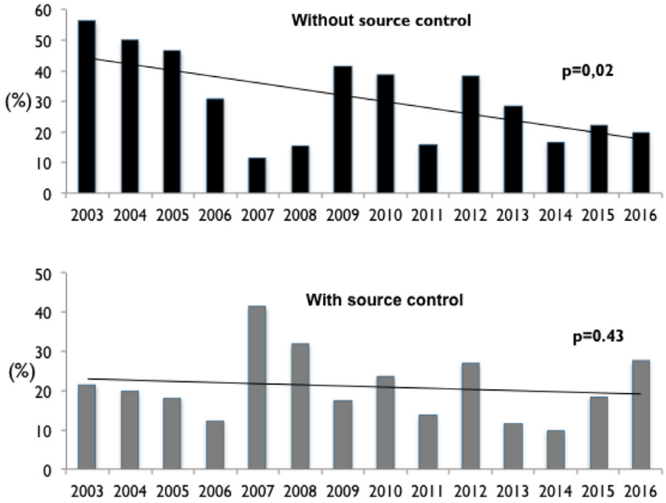


Fig. 2. Mortality trends among patients who did not require source control and among patients who required source control.

studies, probably due to the fact that only patients with community-acquired infection were included and that we used strict criteria to define septic shock (Sepsis-3). Other studies that have analyzed the influence of the change in the definitions of septic shock have found a reduction of almost 40% in cases of septic shock using the definition is Sepsis-3 [16,17].

Concordant with other publications [18,19], the most common source of sepsis was respiratory infection (27%), followed by genitourinary tract infection (22.0%) and intraabdominal infection (20%).

A total of 322 (51.3%) patients required SC, a higher percentage than in other recent studies [19,20]. Martinez et al. [19], evaluating the impact of SC in the evolution of septic shock, reported that 32% required SC. Another prospective observational multicenter study in Germany including 1011 patients with severe sepsis or septic shock reported that 41.7% underwent SC [20]. This difference is likely due to the higher percentage of patients in our study with abdominal, biliary, urogenital, skin, and soft-tissue infections potentially requiring SC (67.7% vs. 57.7% in Martinez et al.'s study and 55.3% in the German study). Most patients (72%) underwent SC interventions within 12 h of septic shock onset, as recommended in the latest Surviving Sepsis Campaign guidelines [21], a rate very similar to the 75.7% in Martinez et al.'s recent study [19].

The crude ICU mortality for septic shock in our study was 25.8%, which is lower than in other studies [22-24] but similar to recent studies about different treatments for septic shock that found no significant differences between control and treated groups (24.2%–32%) [25-27]. More importantly, mortality in the present study decreased from 40% in 2003 to 26.5% in 2016, confirming the trend in decreasing mortality in patients with severe sepsis and septic shock observed in different studies, where the magnitude of the reduction depends on whether clinical or administrative data were used [4-7].

Mortality was lower in the SC group (20.8% vs. 31.3% in patients that did not undergo SC, $p = 0.002$), similar to in Martinez et al.'s study [19], where ICU mortality was 21.2% in patients with SC and 25.1% in patients without SC. We also found that, in patients who underwent required SC, mortality was lower in those undergoing percutaneous/endoscopic interventions (10.4% vs. 26.5% in those undergoing surgical interventions, $p < 0.001$). However, this difference could be attributed mainly to differences in the infection source, since mortality was lower in genitourinary and biliary infections, which are predominantly treated with percutaneous/endoscopic techniques, than in abdominal, skin, and soft-tissue infections, which are predominantly treated with surgical techniques.

In the cases in which the adequacy of SC could be evaluated, SC was adequate in 87.4%, similar to the 86.7% reported by Bloos et al. [20], where 28-day mortality was much higher in patients with inadequate SC (65.5% vs. 26.7% in patients with adequate SC, $p < 0.01$). In the present study, the difference in mortality was even greater (ICU mortality in patients with inadequate SC 84.4% vs. 10.8% in those with adequate SC, $p < 0.001$).

Interestingly, during the study period, mortality among patients who did not require SC decreased from 56.3% in 2003 to 20% in 2016 ($p = 0.02$), even though they significantly had more comorbidities; by contrast, mortality among patients requiring SC did not decrease significantly (21.4% in 2003 to 27.6% in 2016; $p = 0.43$), suggesting that, when required, SC is the most important determinant of pathogen clearance and is therefore the main factor in improving prognosis, whereas patients who do not require SC benefit more from improvements in support treatments, such as, protective ventilation, the application of the recommendations of the sepsis guidelines, to the early diagnosis and treatment of patients with septic shock (resuscitation

Table 4

Prognostic factors associated with ICU mortality (Univariate analysis).

Variable	Alive (n: 464), n (%)	Death (n: 161), n (%)	p
Age, mean (±SD), years	64.86 (14.63)	67.73 (13.89)	0.031
APACHE II, mean (±SD)	19.11 (5.39)	24.83 (7.02)	<0.001
	8.59 (2.27)	10.80 (2.67)	<0.001
Sex			
Male	282 (60.7)	90 (55.9)	0.27
Female	182 (39.2)	71 (44.0)	
Comorbidities			
Diabetes	142 (30.6)	40 (24.8)	0.166
Cancer	93 (20.0)	32 (19.8)	0.96
COPD	63 (13.5)	32 (19.8)	0.05
Alcoholism	32 (6.9)	22 (13.6)	0.09
Dialysis	9 (1.9)	5 (3.1)	0.38
Cirrhosis	20 (4.3)	27 (16.7)	<0.001
Chronic cardiac failure	50 (10.8)	21 (13.0)	0.72
Corticosteroids	36 (7.7)	14 (8.6)	0.70
Immunosuppression	60 (12.9)	18 (11.2)	0.56
Neutropenia	17 (3.7)	5 (3.1)	0.74
HIV	19 (4.1)	5 (3.1)	0.57
Complications			
Acute kidney failure	403 (86.8)	152 (94.4)	0.009
Renal replacement therapy	81 (17.4)	51 (31.7)	<0.001
Thrombocytopenia	275 (59.3)	115 (71.4)	0.005
Mechanical ventilation	259 (55.8)	151 (93.7)	<0.001
ARDS	81 (17.4)	61 (37.8)	<0.001
Bacteremia	238 (51.3)	90 (55.9)	0.31
Microbiology			0.343
Grampositive	136 (29.3)	71 (44.0)	
Gramnegative	208 (44.8)	52 (32.3)	
Anaerobes	9 (1.9)	8 (4.9)	
Fungi	3 (0.6)	1 (0.6)	
Others[a]	3 (0.6)	0 (0)	
Polymicrobial	66 (14.2)	19 (11.8)	
Negative culture	39 (8.4)	10 (6.2)	
Source			<0.001
Respiratory	119 (25.7)	50 (31.0)	
Abdominal	82 (17.7)	43 (26.7)	
Genitourinary	127 (27.4)	11 (6.8)	
Skin and soft tissue	55 (11.8)	25 (15.5)	
Biliary	66 (14.2)	14 (8.7)	
Others[b]	15 (3.2)	18 (11.2)	
Appropriate antibiotic treatment[c]	406 (95.7)	138 (90.7)	0.022
Source control[d]	256 (55.1)	66 (40.9)	0.002
Time of source control <12 h	188 (73.4)	44 (66.6)	0.20
Adequate source control[e]	198 (97.5)	24 (47.0)	<0.001
Type of source control			
Non-invasive	104 (40.6)	12 (17.9)	<0.001
Invasive	152 (59.4)	54 (82.0)	

[a] *Influenza, Mycoplasma pneumoniae, Pneumocystis jirovecii.*

[b] Arthritis, endocarditis, ORL, SNC, unknown origin.

[c] Over 576 patients with positive culture, of which 424 in alive group and 152 in death group.

[d] Over 322 patients with source control.

[e] Over 254 patients who source control could be evaluated as adequate or not, of which 203 in alive group and 51 in death group.

Table 5
Multivariate analysis for independent factors associated with ICU mortality.

Variable	All patients (95% CI)	Patients with source control OR (95% CI)	Patients without source control OR (95% CI)
APACHE II	1.14 (1.10–1.18)	7.93 (2.73–23.0)	1.13 (1.08–1.19)
Cirrhosis	2.69 (1.28–5.66)		3.04 (1.22–7.51)
ARDS	2.54 (1.53–4.21)		2.24 (1.24–4.06)
Age	1.02 (1.00–1.03)		
Thrombocytopenia	1.59 (0.99–2.54)		
Mechanical ventilation		12.17 (1.44–102.35)	
Alcoholism		5.05 (1.14–22.31)	
Appropriate antibiotic treatment	0.38 (0.16–0.87)	0.12 (0.02–0.56)	
Adequate source control		0.02 (0.006–0.78)	

with fluids and early antibiotic treatment) together with a shorter delay in admission to the ICU. More than half of the cases in the group that did not require SC were septic shock secondary to pneumonia and therefore these results would confirm those recently published by our group on the progressive improvement in mortality of patients with severe community-acquired pneumonia [28].

Among comorbidities, only alcoholism and cirrhosis were independently associated with ICU mortality. Although in recent years the prognosis of patients with septic shock and cirrhosis has improved [29], our results confirm that this comorbidity significantly increases the risk of poor outcome in patients with septic shock. Alcoholism is also associated with an increased severity of multiple organ dysfunction in patients with septic shock [30]. Finally, our results corroborate previous findings that ARDS and thrombocytopenia were independently associated with poor prognosis in patients with septic shock [31,32] and the importance of appropriate empiric antibiotic treatment and adequate SC in reducing mortality in these patients [9,33,34].

Chief among the various limitations of our study is its retrospective design. Moreover, this was a single-center study, so its results cannot be extrapolated to other populations in hospitals with different characteristics. On the other hand, although we adjusted for a number of predisposing patient factors, there may be other confounding factors that we did not measure. Furthermore, during the years included in the study, the ICU admission criteria may have varied and therefore influenced the incidence of community-acquired septic shock in the ICU population. Nevertheless, our study also has strengths. We used the Sepsis-3 definitions to uniformly select a large cohort of patients with high severity from a long period. Patients were monitored until death or hospital discharge, resulting in a homogeneous database with high-quality control measures to ensure validity. Cases of sepsis were identified by clinical data rather than indirectly by using ICD-9-CM codes, increasing the accuracy of identification. Finally, 92.2% of patients had positive cultures and blood cultures were positive in 52.5%, which confirms the infectious origin of the shock.

5. Conclusions

Our study found a progressive increase in the incidence of patients with CASS admitted to our ICU in recent years and a progressive decrease in associated mortality. The decrease in mortality was mainly due to better outcomes in infections that did not require SC, suggesting an improvement in the management of patients with septic shock. Administering appropriate empirical antibiotic treatment and adequate SC as early as possible is important for survival in septic shock. Older age, alcoholism, and cirrhosis, together with the severity at admission and organic dysfunctions due to shock, are associated with worse prognosis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statements

The authors confirm that they have no conflicts of interest in the elaboration of this article.

Acknowledgment

We thank Ana Villagrá MD for reviewing the manuscript.

References

[1] Quenot JP, Binquet C, Kara F, Martinet O, Ganster F, Navellou JC, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care 2013;17:R65. https://doi.org/10.1186/cc12598.

[2] Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 2014;311:1308–16. https://doi.org/10.1001/jama.2014.2637.

[3] Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the surviving Sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis 2012;12:919–24. https://doi.org/10.1016/S1473-3099(12)70239-6.

[4] Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med 2014;42:625–31. https://doi.org/10.1097/CCM.0000000000000026.

[5] Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyma TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA 2017;318:1241–9. https://doi.org/10.1001/jama.2017.13836.

[6] Rhee C, Kadri S, Huang S, Murphy MV, Li L, Platt R, et al. Objective sepsis surveillance using electronic clinical data. Infect Control Hosp Epidemiol 2016;37:163–71. https://doi.org/10.1017/ice.2015.264.

[7] Kadri S, Rhee C, Strich J, Morales MK, Hohmann S, Menchaca J, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. Chest 2017;151:278–85. https://doi.org/10.1016/j.chest.2016.07.010.

[8] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/jama.2016.0287.

[9] Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2013;123:1615–24 [PMID: 12740282].

[10] Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care 2013;17(1):204. https://doi.org/10.1186/cc11454.

[11] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10 [PMID: 8844239].

[12] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. ARDS Definition Task Force JAMA 2012;307:2526–33. https://doi.org/10.1001/jama.2012.5669.

[13] Knaus WA, Draper EA, Wagner DP, Zimmerman JE, Bergner M, Bastos PG, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29 [PMID:1959406].

[14] Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 2012;10(6):701–6. https://doi.org/10.1586/eri.12.50.

[15] Girard TD, Opal SM, Ely EW. Insights into severe sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis 2005;40(5):719–27. https://doi.org/10.1086/427876.

[16] Driesen RGH, van de Poll MCG, Mol MF, van Mook WNKA, Schnabel RM. The influence of a change in septic shock definitions on intensive care epidemiology and outcome: comparison of sepsis-2 and sepsis-3 definitions. Infect Dis (Lond) 2018;50:207–13. https://doi.org/10.1080/23744235.2017.1383630.

[17] Fernando SM, Reardon PM, Rochwerg B, Shapiro NI, Yealy DM, Seely AJE, et al. Sepsis-3 septic shock criteria and associated mortality among infected hospitalized

patients assessed by a rapid response team. Chest 2018;154:309–16. https://doi.org/10.1016/j.chest.2018.05.004.

[18] Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, et al. Timing and causes of death in septic shock. Ann Intensive Care 2015;5:16. https://doi.org/10.1186/s13613-015-0058-8.

[19] Martinez ML, Ferrer R, Torrents E, Guillamat-Prats R, Gomà G, Suárez D, et al. Impact of source control in patients with severe sepsis and septic shock. Crit Care Med 2017;45:11–9. https://doi.org/10.1097/CCM.0000000000002011.

[20] Bloos F, Thomas-Rüddel D, Rüddel H, Engel C, Swarchkopf D, Marshall JC, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care 2014; 18:R42. https://doi.org/10.1186/cc13755.

[21] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637. https://doi.org/10.1097/CCM.0b013e31827e83af.

[22] Leligdowicz A, Dodek PM, Norena M, Wong H, Kumar A, Kumar A. Association between source of infection and hospital mortality in patients who have septic shock. Am J Respir Crit Care Med 2014;189:1204–13. https://doi.org/10.1164/rccm.201310-1875OC.

[23] Alberti C, Brun-Buisson C, Goodman SV, Guidici D, Granton J, Moreno R, et al. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. Am J Respir Crit Care Med 2003;168:77–84. https://doi.org/10.1164/rccm.200208-785OC.

[24] Annane D, Aegerter P, Jars-Guincestre MC, Guidet B, Network CUB-Rea. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003; 168:165–72. https://doi.org/10.1164/rccm.2201087.

[25] Ranieri VM, Thompson T, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366:2055–64. https://doi.org/10.1056/NEJMoa1202290.

[26] Opal SM, Laterre PF, Francois B, La Rosa SP, Angus DC, Mira JP, et al. Effect of eritoran, an agonist of MD2-TLR4, on mortality in patients with severe sepsis. The ACCESS randomized trial. JAMA 2013;309:1154–62. https://doi.org/10.1001/jama.2013.2194.

[27] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014;370: 1412–21. https://doi.org/10.1056/NEJMoa1305727.

[28] Vallés J, Díaz E, Martín-Loeches I, Bacelar N, Saludes P, Lema J, et al. Evolution over a 15-year period of the clinical characteristics and outcomes of critically ill patients with severe community-acquired pneumonia. Med Intensiva 2016;40:238–45. https://doi.org/10.1016/j.medin.2015.07.005.

[29] Galbois A, Aegerter P, Martel-Samb P, Housset C, Thabut D, Offenstadt G, et al. Improved prognosis of septic shock in patients with cirrhosis: a multicenter study. Crit Care Med 2014;42:1666–75. https://doi.org/10.1097/CCM.0000000000000321.

[30] Moss M, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Nunham EL, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med 2003;31:869–77. https://doi.org/10.1097/01.CCM.0000055389.64497.11.

[31] Zilberberg MD, Epstein SK. Acute lung injury in the medical ICU. Comorbid conditions, age, etiology, and hospital outcome. Am J Respir Crit Care Med 1998;157: 1159–64. https://doi.org/10.1164/ajrccm.157.4.9704088.

[32] Thiery-Antier N, Binquet C, Vinault S, Meziani F, Boisramé-Helms J, Quenot JP. EPIdemiology of septic shock group. Is thrombocytopenia an early prognostic marker in septic shock? Crit Care Med 2016;44:764–72. https://doi.org/10.1097/CCM.0000000000001520.

[33] Valles J, Palomar M, Alvarez-Lerma F, Rello J, Blanco A, Garnacho-Montero J, et al. Evolution over a 15-year period of clinical characteristics and outcomes of critically ill patients with community-acquired bacteremia. Crit Care Med 2013;41:76–83. https://doi.org/10.1097/CCM.0b013e3182676698.

[34] Kreger BE, Craven DE, McCabe WR. Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 1980;68:344–55 [PMID:6987871].