International Journal of Infectious Diseases 58 (2017) 52–57

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Sepsis-related mortality in 497 cases with blood culture-positive sepsis in an emergency department

Juha Rannikko[a,*], Jaana Syrjänen[a], Tapio Seiskari[b], Janne Aittoniemi[b], Reetta Huttunen[a]

[a] Department of Internal Medicine, Tampere University Hospital, Box 2000, FI-33521 Tampere, Finland
[b] Department of Clinical Microbiology, Fimlab Laboratories, Tampere, Finland

ARTICLE INFO

Article history:
Received 14 December 2016
Received in revised form 15 February 2017
Accepted 5 March 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Attributable mortality
Blood culture
Infectious disease
Related mortality
Sepsis
Survival
qSOFA

SUMMARY

Objective: Few studies have sought to establish how often death after sepsis is related to the sepsis and how often underlying diseases have a major role in case fatality.
Methods: In this retrospective cohort study, data were collected on 497 cases with blood culture-positive sepsis in an emergency department (ED).
Results: Sepsis was categorized as severe in 31% of cases; 7% had septic shock. The quick Sepsis-related Organ Failure Assessment score was positive in 136 out of 473 cases (29%). Ninety-eight patients died by day 90; in 16 of these cases (16%) the death was sepsis-related in a patient without a rapidly fatal underlying disease, in 45 cases (46%) the death was sepsis-related in a patient with a rapidly fatal underlying disease, and in 37 cases (38%) the death was unrelated to sepsis. Sepsis-related death occurred in 58 out of 61 cases (95%) by day 28.
Conclusions: Underlying diseases were found to have a considerable role in the death of patients suffering from blood culture-positive sepsis in an ED of a developed country, as only 16% of the deaths by day 90 occurred where death was sepsis-related and the patient had a life-expectancy of more than 6 months. Improving the outcome of sepsis with new treatments is thus challenging. It is possible that day 7 + day 28 mortality is a more appropriate endpoint than day 90 mortality when studying the outcome of sepsis, as this time-span includes most of the patients whose death was related to sepsis.

Introduction

Sepsis is one of the leading causes of death worldwide. It has been ranked as the eleventh most common cause of death in the USA.[1] Advanced age, immunosuppression, diabetes, and cancer are major risk factors for sepsis.[2–6] Prognostic factors for the severity and outcome of sepsis include advanced age, type of infection (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA), polymicrobial), number of organ dysfunctions, and adequacy of antimicrobial therapy.[7–9]

Studies have been performed on sepsis patients in emergency departments (EDs) and intensive care units (ICUs) in order to determine risk factors for mortality[9–13] and the aetiology of illness.[14] Less attention has been paid to the questions of how often these patients actually die of sepsis, how often sepsis is a contributory factor in the death of a patient with an advanced underlying disease, and how often the death is independent of sepsis.

In this retrospective cohort study, data were collected on 497 adult cases of blood culture-positive sepsis in the ED of Tampere University Hospital (TAUH). A categorization of causes of death was developed in order to establish how often death was related to sepsis in patients without a rapidly fatal underlying disease (group 1), was related to sepsis by weakening of a patient with a rapidly fatal underlying disease (group 2), and was independent of sepsis but caused by the underlying disease (group 3). It was also sought to determine the best cut-off among the commonly used days for mortality used in sepsis research, i.e. day 7, day 28, or day 90, for mortality related to sepsis (deaths in groups 1 and 2).

Materials and methods

TAUH is a tertiary hospital with a catchment population of approximately 524 700 inhabitants in Pirkanmaa County. The ED of

* Corresponding author. Tel: +358 3 31166747, Fax: +358 3 31164333.
E-mail address: juha.rannikko@gmail.com (J. Rannikko).

http://dx.doi.org/10.1016/j.ijid.2017.03.005

the hospital handles patients requiring both basic and specialized emergency care. In specialized care, the majority of patients are internal medicine and surgical patients. Blood cultures are taken routinely from patients with signs or symptoms of systemic infection. The population of the present study comprised 497 adult patients admitted to the ED of TAUH and treated in specialized care, who had blood culture-positive sepsis during the period March 1, 2012 to February 28, 2014. The study was approved by the Ethics Committee of Tampere University Hospital. The need for informed consent was waived, as no additional blood sampling was needed and routine patient care was not modified.

TAUH has a 24-bed ICU which includes a seven-bed high dependency unit (HDU). In this article, 'ICU' refers to both of these. There are four other HDUs (cardiology, pulmonary, surgical, and internal medicine), all taking care of sepsis patients; these are referred to as 'HDUs'.

Blood cultures were collected in BacT/Alert Aerobic (FA Plus) and Anaerobic (FN Plus) blood culture bottles and placed in the automated microbial detection system BacT/Alert 3D (bioMérieux, Marcy l'Etoile, France). All patients with a positive blood culture obtained during specialized care in the ED were identified in the microbiology laboratory serving TAUH (Fimlab Laboratories plc). Patient details, the name of the organism, and the date of blood culture were collected by clinical microbiologists (T.S. and J.A.). Cultures positive for coagulase-negative Staphylococcus, Propionibacterium, Micrococcus, Bacillus, and Corynebacterium, with detection in a single blood culture bottle and without clinical relevance, were considered to be contaminants and were excluded.

Patients whose routine blood samples taken on admission were no longer available for further studies were also excluded. This could be due, for example, to the fact that the blood culture became positive later than 72 h after the day of admission.

The clinical data for the patients included in the study were gathered retrospectively from the patient records by the principal investigator (J.R.). The site of infection was decided retrospectively by the principal investigator based on clinical judgement. Sepsis was deemed to be healthcare-associated if the symptoms had started more than 48 h after admission to a healthcare institution, or the bacteraemia was related to a surgical operation within the preceding 30 days or some other invasive procedure within the previous 10 days.[15] Data on cause of death were gathered from patient records (and autopsy records when applicable) by two clinicians (J.R. and R.H.) independently. In cases of discrepancy, a meeting was held together with a third clinician (J.S.) and a final decision was made.

Cause of death by day 90 was classified into three different categories: (1) group 1 included cases of sepsis-related mortality in patients without a rapidly fatal underlying disease. The immediate cause of death in this group was sepsis, or sepsis was a factor in a chain of events leading to death, and the patient had a life-expectancy of more than 6 months. (2) Group 2 included cases of sepsis-related mortality in patients with a rapidly fatal underlying disease. In this group, the patient died of sepsis (immediate cause of death, or sepsis was a factor in a chain of events leading to death) by weakening of a patient with a rapidly fatal (<6 months) underlying disease. (3) Group 3 included cases of mortality related to underlying disease. In this group, sepsis was not an immediate cause of death or a factor in a chain of events leading to death.

The categorization was based on clinical decision and the judgement was based on the severity of the patient's underlying disease, the patient's pre-performance, severity of the sepsis, and recovery after the infection. The main underlying disease associated with death was determined retrospectively by the principal investigator.

Diagnoses of sepsis, severe sepsis, and septic shock were made according to consensus definitions.[16] Further, the quick Sepsis-related Organ Failure Assessment score (qSOFA) was calculated post-hoc according to recently published definitions.[17] The qSOFA score was positive if at least two of the following three criteria were fulfilled in the ED: respiratory rate ≥22/min, altered mentation, and systolic blood pressure ≤100 mmHg. The McCabe classification was determined as reported by McCabe and Jackson.[18] The Pitt bacteraemia score was calculated as presented by Korvick et al.[19] IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Categorical data were analyzed by Chi-square test, or Fisher's exact test when appropriate. Odds ratios (OR) with 95% confidence intervals (95% CI) are also presented.

Results

There were 800 consecutive positive blood cultures in adult patients during the study period. One hundred and thirty-six of these were considered to be contaminants and 167 were excluded for other reasons. A total 497 cases of positive blood culture among 484 patients were thus included. All 497 cases had sepsis. During the study period, 11 patients had sepsis twice on different admissions and one patient had sepsis three times. Of the total study population, 262 (53%) were male and 235 (47%) were female; they ranged in age from 16 to 95 years (median 68 years).

Table 1 provides the demographic data, data on the causative organisms, and data on the underlying diseases stratified into six different categories: groups 1, 2, and 3 (as noted in the Materials and methods section), all patients who died, all patients who survived, and all cases. For 16 out of 98 patients (16%) who died by day 90, death was related to sepsis and the patient did not have a rapidly fatal underlying disease (group 1), i.e. 3% of all 497 sepsis cases. For 45 patients (46% of all deaths by day 90), death was related to sepsis in that it weakened the patient leading to the death, which was in any case expected as the patient had a rapidly fatal underlying disease (group 2). For 37 patients (38%), death by day 90 was unrelated to sepsis and was caused by an underlying disease(s) in the patient (group 3).

Of the group 1 patients, four (25%) had alcohol abuse as an underlying disease (Table 1). One was without any underlying disease. Four of the patients in group 1 were over 80 years of age (25%). Three group 1 patients (19%) were found lying at home with a low level of consciousness and were transferred to hospital. In group 2 patients, the rapidly fatal underlying disease was a solid tumour with metastasis in eight cases (18%) and a haematological malignancy in nine (20%). In group 3 patients, the cause of death was a solid tumour with metastasis in 19 patients (51%) and a haematological malignancy in two (5%). Thus, malignancies were associated with death in 46% of patients in groups 2 and 3 combined. Other common rapidly fatal underlying diseases associated with death among the patients in groups 2 and 3 were liver disease (11%), heart disease (11%), and neurological/neurosurgical disease (10%).

The case fatality rate by day 7, day 28, and day 90 was 9%, 14%, and 20%, respectively. Death occurred by day 7 in 94% of group 1 patients, in 56% of group 2 patients, and in 11% of group 3 patients (Figure 1). All except two cases in group 2 died before day 28. The deaths in group 3 occurred most often between day 29 and day 90 (68%). Ninety-five per cent of all sepsis-related deaths occurred within 28 days after sepsis.

Table 2 gives data on the severity of sepsis stratified into the same categories as used in Table 1. The qSOFA was positive in 136 out of 473 cases (29%). Group 1 had the highest Pitt bacteraemia scores. Forty-eight (10%) cases were transferred from the ED to the ICU and 52 (11%) to HDUs. Thus, the majority of sepsis patients and the majority of qSOFA-positive cases were taken care of in general wards. Out of 449 cases who were treated outside the ICU, 104

Table 1
Characteristics underlying diseases, and causative organisms in relation to the outcome.

	Sepsis-related mortality in patients without a rapidly fatal underlying disease (Group 1) (*n* = 16) *n* (%)	Sepsis-related mortality in patients with a rapidly fatal underlying disease (Group 2) (*n* = 45) *n* (%)	Mortality related to underlying disease (Group 3) (*n* = 37) *n* (%)	All patients who died (*n* = 98) *n* (%)	Patients who survived (*n* = 399) *n* (%)	All cases (*N* = 497) *n* (%)
Median age, years (range)	77 (51–94)	78 (42–93)	70 (44–91)	74 (42–94)	68 (16–95)	68 (16–95)
Male sex	8 (50)	24 (53)	25 (68)	57 (58)	205 (51)	262 (53)
Underlying diseases						
Heart disease	8 (50)	23 (51)	10 (27)	41 (42)	135 (34)	176 (35)
Diabetes mellitus, any type	6 (38)	15 (33)	13 (35)	34 (34)	105 (26)	139 (28)
Neurological	5 (31)	14 (31)	9 (24)	28 (29)	84 (21)	112 (23)
Solid tumour with metastasis[a]	1 (6)	10 (22)	17 (46)	28 (29)	29 (7)	57 (12)
Alcohol abuse[b]	4 (25)	5 (11)	8 (22)	17 (17)	35 (9)	52 (11)
Liver disease	3 (19)	8 (18)	6 (16)	17 (17)	32 (8)	49 (10)
Haematological malignancy	0 (0)	11 (24)	4 (11)	15 (15)	30 (8)	45 (9)
No underlying diseases	1 (6)	0 (0)	0 (0)	1(6)	70 (14)	71 (14)
Causative organism[c]						
Gram-positive	5 (31)	18 (40)	13 (35)	36 (37)	189 (47)	225 (45)
Gram-negative	9 (56)	19 (42)	14 (38)	42 (43)	181 (45)	223 (45)
Escherichia coli urosepsis	3 (19)	6 (13)	3 (8)	12 (12)	85 (21)	97 (20)
Polymicrobial and anaerobes	2 (13)	8 (18)	10 (27)	20 (20)	28 (7)	48 (10)

[a] The most common solid tumour with metastasis was cancer of the gastrointestinal tract (36 cases).
[b] Social or medical problems of alcohol abuse in the past 12 months.
[c] Excluding fungi (*n* = 1).

(23%) had severe sepsis and nine (2%) had septic shock. Of those with septic shock, three died in the ED and the remainder had underlying diseases that had progressed too far for them to benefit from treatment in the ICU.

By site of infection, the most common infection was urinary tract infection (131 cases, 26%), followed by intra-abdominal infection (84 cases, 17%), infection of the skin, soft tissues, and bones (72 cases, 15%), and lower respiratory tract infection (54 cases, 11%). The site of infection was unknown in 118 cases

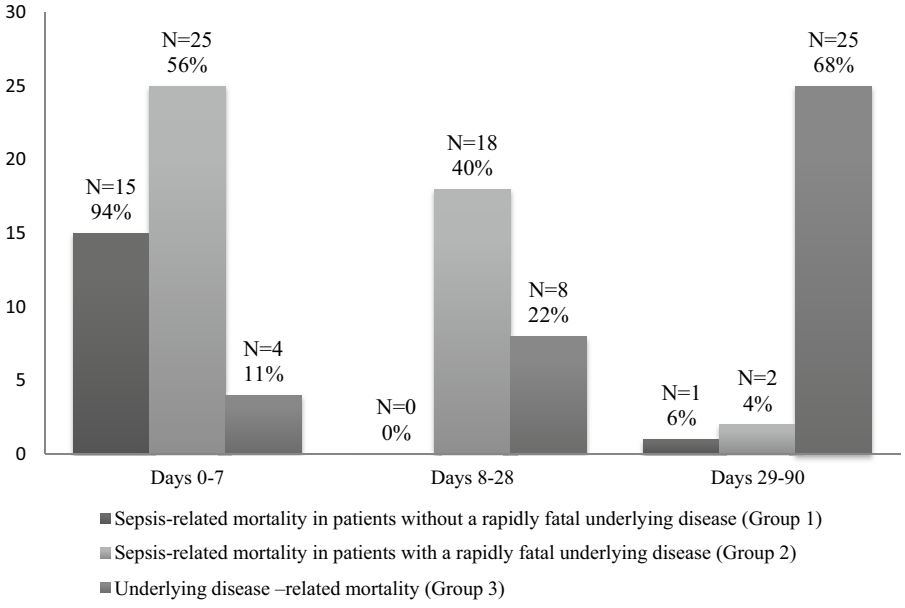

Figure 1. Number of cases in groups 1, 2, and 3 in relation to day of case fatality in a total of 98 patients who died within 90 days after sepsis. The percentage is per category of cause of death.

Table 2
Severity of the sepsis in relation to the outcome.

	Sepsis-related mortality in patients without a rapidly fatal underlying disease (Group 1) (n = 16)	Sepsis-related mortality in patients with a rapidly fatal underlying disease (Group 2) (n = 45)	Mortality related to underlying disease (Group 3) (n = 37)	All patients who died (n = 98)	Patients who survived (n = 399)	All cases (N = 497)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Severe sepsis	16 (100)	30 (67)	13 (35)	59 (60)	93 (23)	152 (31)
Septic shock	9 (56)	9 (20)	4 (11)	22 (22)	15 (4)	37 (7)
qSOFA-positive[a]	13 (81)	26 (59)	16 (46)	55 (58)	81 (21)	136 (29)
Admitted from ED to ICU	11 (69)	7 (16)	3 (8)	21 (21)	27 (7)	48 (10)
Pitt bacteraemia score[b]						
0–1	1 (6)	16 (36)	20 (57)	37 (39)	269 (68)	306 (62)
2–3	3 (19)	17 (39)	10 (29)	30 (32)	93 (24)	123 (25)
≥4	12 (75)	11 (25)	5 (14)	28 (29)	33 (8)	61 (12)

ED, emergency department; ICU, intensive care unit; qSOFA, quick sepsis-related organ failure assessment.
[a] Data available for 473 cases (95 who died and 378 who survived).
[b] Data available for 490 cases.

(24%). Sepsis was healthcare-associated in 81 patients (16%). The previous use of immunosuppressive medications was common: 94 (19%) patients were taking corticosteroids (any dose) and 56 (11%) were on cancer chemotherapy. Antibiotics were started on the day of admission in 93% of patients. The most common antibiotic was cefuroxime (57%), followed by ceftriaxone (18%) and fluoroquinolone (11%). An antibiotic combination was started in 16% of patients. The median time from admission to the start of antibiotics was 174 min (range 0–1269 min).

Of all cases, 426 (86%) had one or more underlying diseases. As shown in Table 1, there were significantly more alcohol abusers in group 1 as compared to those who survived for more than 90 days (4/16 vs. 35/399; OR 3.8, 95% CI 1.2–12.4, p = 0.04). There were also significantly more patients with a solid tumour with metastasis and patients with haematological malignancies among those who died by day 90 than among survivors (28/98 vs. 29/399, OR 5.1, 95% CI 2.9–9.1, $p < 0.01$ and 15/98 vs. 30/399, OR 2.2, 95% CI 1.1–4.3, p = 0.02, respectively).

The causative organisms are listed in Table 3. Gram-positive and Gram-negative organisms were equally common. There were few cases with MRSA and extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and no cases with vancomycin-resistant enterococci or carbapenemase-producing *Enterobacteriaceae*.

Table 3
Causative organisms.

Organisms	n (%)
Gram-positive	225 (45.3)
Staphylococcus aureus	74 (14.9)
MRSA	3 (0.6)
Coagulase-negative Staphylococcus	11 (2.2)
Streptococcus pneumoniae	52 (10.5)
β-haemolytic streptococci	45 (9.1)
Viridans streptococci	21 (4.2)
Enterococci	17 (3.4)
Other Gram-positive	5 (1.0)
Gram-negative	223 (44.9)
Escherichia coli	159 (32.0)
ESBL-*E. coli*	9 (1.8)
Klebsiella sp	21 (4.2)
ESBL-*Klebsiella sp*	0 (0.0)
Pseudomonas aeruginosa	18 (3.6)
Other Gram-negative	25 (5.0)
Others	49 (9.9)
Anaerobes	15 (3.0)
Fungi	1 (0.2)
Polymicrobial	33 (6.6)
All	497 (100)

MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamase.

Discussion

In this study, the case fatality rate by day 7, day 28, and day 90 was 9%, 14%, and 20%, respectively, in 497 cases with blood culture-positive sepsis treated in an ED. The day 7 and day 28 case fatality rates in this study are similar to those reported in a study by Lin et al., who also studied bacteraemic patients in the ED.[9] In two other studies investigating the day 28 case fatality rate in bacteraemic patients in the ED, Lee et al. reported a rate of 9% and Kao et al. reported a rate of 19%.[12,20]

Only 16% of all deaths by day 90 in the present study were related to sepsis in patients with a life-expectancy of more than 6 months (group 1). Forty-six percent of deaths occurred in patients with a rapidly fatal underlying disease although death was sepsis-related (group 2), and 38% of deaths were related to the underlying disease (group 3). It is known that underlying diseases have a role in the deaths of sepsis patients,[2–4,9] but the categorization of the present study gives a picture of the significance of the underlying diseases in these deaths.

Even patients in group 1 had many factors contributing to death, for example alcoholism or very old age. There was only one patient in this group without any underlying disease. It is possible that there were patients in group 1 who sought treatment too late, as three patients in this group were found lying at home with a low level of consciousness. There were also significantly more alcohol abusers as compared to those who survived more than 90 days. Altogether, in this cohort consisting mostly of community-acquired cases seen in a university hospital ED in a developed country, there were few non-survivors who would have had a life-expectancy of more than 6 months and who might have benefited from a novel drug directed against sepsis or septic shock. This may also explain why so many clinical trials in the field of sepsis have failed.[21]

Day 90 mortality has been used as the endpoint in many sepsis studies.[22–24] However, the present study showed that most (95%) of the patients whose death was sepsis-related died within 28 days after sepsis, while the majority of deaths occurring between day 28

and day 90 were independent of sepsis. This makes day 28 a more appropriate time-point to investigate sepsis-related mortality, as regulatory agencies have indeed considered.[21] Nonetheless, only 34% of deaths occurring between day 0 and day 7 were sepsis-related in patients with a life-expectancy of more than 6 months. Thus, even when day 7 and day 28 are used as endpoints for sepsis mortality, deaths independent of sepsis are not ruled out.

This study has some limitations. By reason of the study design, it was not possible to include all blood culture-positive cases admitted to the ED during the study period. The potential representativeness of the material was assessed by reviewing the blood culture findings of those cases that were not included in the study. Altogether there were 167 such cases (contaminants excluded). The percentages of the most common blood culture findings, *S. aureus* and *Escherichia coli*, did not differ between the study population and the cases that were not included. It is thus unlikely that missed cases would have had a major impact on the results. Among cases not included in the material as compared to those included, the percentage of anaerobes and other Gram-negative organisms (see Table 3) was somewhat higher (9.0% vs. 3.0% and 10.2% vs. 5.0%, respectively) and the percentage of *Streptococcus pneumoniae* was lower (4.2% vs. 10.5%). This may be due to the long incubation period of anaerobes and other Gram-negative organisms and the short incubation period of *S. pneumoniae*. Again, assuming that case fatality among missed cases with anaerobes or other Gram-negatives would be approximately the same as among those included in the study, the numbers would be too low to alter the major findings of the study.

Only blood culture-positive cases were included, which would exclude for example those with false-negative blood cultures. This might also have led to a lower number of septic patients with respiratory infection. However, it is also a strength that culture-negative sepsis cases, which are difficult to define, were not included. Hence the material consists more of true infections than patients who were for example only positive for systemic inflammatory response syndrome (SIRS).

The material was gathered in a tertiary level hospital of a developed country with a low incidence of multi-resistant bacteria. These types of results cannot, therefore, be generalized to low-income countries, as has been pointed out by Rello and Leblebicioglu.[25] It is possible that the role of the underlying diseases would also have been different if the study patients had been only from ICUs.

The method used to categorize the cause of death was developed by the authors. It encompasses the classification used on the death certificate (immediate cause and underlying cause) and combines it with the McCabe classification of rapidly fatal disease. This has limitations, since in some cases it was not easy to decide whether the patient would have lived for more than 6 months without the sepsis or not. Even group 1 patients were elderly and had many underlying diseases. However, the authors believe that the categorization used is illustrative of the course of events among these patients, and the use of two or three clinicians to provide a judgement gives it sufficient validity.

In conclusion, this study showed that patients with sepsis who die within 90 days after sepsis in a developed country, die mostly either of sepsis by weakening of the patient with a rapidly fatal (<6 months) underlying disease, or of the underlying disease itself. This does not mean that sepsis patients do not need high-quality care. Indeed, the low number of cases of sepsis-related mortality among patients with a life-expectancy of more than 6 months may be attributed to the good quality of the care these patients received. When investigating sepsis-related mortality, day 28 should be used as the endpoint to identify most of the sepsis-related mortality, while a large part of sepsis-independent mortality is ruled out.

Funding

This work was supported by the Competitive Research Financing of Tampere University Hospital (grant 9N075 to J.R. and X50060 to J.A.). The authors' work was independent of the funder (the funding source had no involvement).

Ethical approval

The study was approved by the Ethics Committee of Tampere University Hospital.

Conflict of interest

JR, JS, TS, JA, and RH report no conflict of interest.

References

1. K.D. Kochanek, S.L. Murphy, J. Xu, B. Tejada-Vera, Deaths: final data for 2014, Natl Vital Stat Rep. 2016; 65(June (4)):1–122.
2. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006;**34**:15–21.
3. Williams MD, Braun LA, Cooper LM, Johnston J, Weiss RV, Qualy RL, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care Med* 2004;**8**:R291–8.
4. Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Chronic medical conditions and risk of sepsis. *PLoS One* 2012;**7**:e48307.
5. Torres VB, Azevedo LC, Silva UV, Caruso P, Torelly AP, Silva E, et al. Sepsis-Associated Outcomes in Critically Ill Patients with Malignancies. *Ann Am Thorac Soc* 2015;**12**:1185–92.
6. Novosad SA, Sapiano MR, Grigg C, Lake J, Robyn M, Dumyati G, et al. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. *MMWR Morb Mortal Wkly Rep* 2016;**65**:864–9.
7. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589–96.
8. Karlsson S, Varpula M, Ruokonen E, Pettila V, Parviainen I, Ala-Kokko TI, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med* 2007;**33**:435–43.
9. Lin JN, Tsai YS, Lai CH, Chen YH, Tsai SS, Lin HL, et al. Risk factors for mortality of bacteremic patients in the emergency department. *Acad Emerg Med* 2009;**16**:749–55.
10. Ortega M, Almela M, Martinez JA, Marco F, Soriano A, Lopez J, et al. Epidemiology and outcome of primary community-acquired bacteremia in adult patients. *Eur J Clin Microbiol Infect Dis* 2007;**26**:453–7.
11. Gille-Johnson P, Hansson KE, Gardlund B. Clinical and laboratory variables identifying bacterial infection and bacteraemia in the emergency department. *Scand J Infect Dis* 2012;**44**:745–52.
12. Lee CC, Lee CH, Chuang MC, Hong MY, Hsu HC, Ko WC. Impact of inappropriate empirical antibiotic therapy on outcome of bacteremic adults visiting the ED. *Am J Emerg Med* 2012;**30**:1447–56.
13. Blanco J, Muriel-Bombin A, Sagredo V, Taboada F, Gandia F, Tamayo L, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit Care* 2008;**12**:R158.
14. Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. *Clin Infect Dis* 2010;**50**:814–20.
15. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309–32.
16. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250–6.
17. 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.
18. McCabe W, Jackson G. Gram-Negative Bacteremia; I. Etiology and Ecology. *Arch Intern Med* 1962;**110**:847–55.
19. Korvick JA, Marsh JW, Starzl TE, Yu VL. Pseudomonas aeruginosa bacteremia in patients undergoing liver transplantation: an emerging problem. *Surgery* 1991;**109**:62–8.
20. Kao CH, Kuo YC, Chen CC, Chang YT, Chen YS, Wann SR, et al. Isolated pathogens and clinical outcomes of adult bacteremia in the emergency department: a retrospective study in a tertiary Referral Center. *J Microbiol Immunol Infect* 2011;**44**:215–21.
21. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med* 2014;**20**:195–203.

22. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;**367**:124–34.
23. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;**370**:1683–93.
24. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;**358**:877–87.
25. Rello J, Leblebicioglu H. Sepsis and septic shock in low-income and middle-income countries: need for a different paradigm. *Int J Infect Dis* 2016;**48**:120–2.