Clinical Microbiology and Infection 25 (2019) 326–331

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Impact of antibiotic administration on blood culture positivity at the beginning of sepsis: a prospective clinical cohort study

C.S. Scheer [1, *], C. Fuchs [1], M. Gründling [1], M. Vollmer [2], J. Bast [3], J.A. Bohnert [4], K. Zimmermann [4], K. Hahnenkamp [1], S. Rehberg [1], S.-O. Kuhn [1, *]

[1] Department of Anesthesiology, University Hospital Greifswald, Germany
[2] Institute of Bioinformatics, University Hospital Greifswald, Germany
[3] Medical Faculty, University of Greifswald, Germany
[4] Friedrich Loeffler Institute of Medical Microbiology, University Hospital Greifswald, Germany

Mark Crislip podcast May 15-31 2019: "By 2 hours after antibiotics, the positive rate is reduced by at least 50%. May remain positive up to 6 hrs after antibiotics. NB. Staph. aureus will not drop after antibiotics as much as it is difficult to kill.

ARTICLE INFO

Article history:
Received 15 March 2018
Received in revised form
9 May 2018
Accepted 12 May 2018
Available online 4 June 2018

Editor: L. Leibovici

Keywords:
Antibiotic therapy
Blood culture
Pathogen
Positivity
Sepsis

ABSTRACT

Objectives: Sepsis guidelines recommend obtaining blood cultures before starting anti-infective therapy in patients with sepsis. However, little is known of how antibiotic treatment before sampling affects bacterial growth. The aim of this study was to compare the results of blood cultures drawn before and during antibiotic therapy.

Methods: Prospective clinical cohort study of septic patients. Adult intensive care unit patients with two or three blood culture sets at the beginning of sepsis between 2010 and 2017 were included. Patients with blood culture samples obtained before antibiotic therapy were compared with patients with samples taken during antibiotic therapy. Blood culture positivity, defined as presence of a microbiological pathogen, was compared between the groups. Logistic regression was performed to adjust the impact of different factors with respect to blood culture positivity.

Results: In total, 559 patients with 1364 blood culture sets at the beginning of sepsis were analysed. Blood culture positivity was 50.6% (78/154) among patients with sepsis who did not receive antibiotics and only 27.7% (112/405) in those who were already receiving antibiotics ($p < 0.001$). Logistic regression revealed antibiotic therapy as an independent factor for less pathogen identification (odds ratio 0.4; 95% CI 0.3–0.6). Gram-positive pathogens (28.3% (111/392) versus 11.9% (116/972); $p < 0.001$) and also Gram-negative pathogens (16.3% (64/392) versus 9.3% (90/972); $p < 0.001$) were more frequent in blood culture sets drawn before antibiotic therapy compared with sets obtained during antibiotic therapy.

Conclusions: Obtaining blood cultures during antibiotic therapy is associated with a significant loss of pathogen detection. This strongly emphasizes the current recommendation to obtain blood cultures before antibiotic administration in patients with sepsis. **C.S. Scheer, Clin Microbiol Infect 2019;25:326**

Introduction

Appropriate microbiological diagnosis in patients with sepsis includes blood cultures (aerobic and anaerobic) for the detection of bloodstream pathogens and supports adaptation of antibiotic therapy and de-escalation strategies [1]. Although blood cultures are a key element of the surviving sepsis campaign sepsis bundles and are rated as 'best practice statement' in current guidelines [2], studies investigating the impact of antibiotic administration on blood culture positivity at the beginning of sepsis are lacking. Recommendations of recent guidelines [2] are mainly based on a study that investigated the impact of antibiotic pretreatment on pathogens in cerebrospinal fluids in children [3] and an experimental study comparing two different blood culture media [4].

Further evidence can only be obtained indirectly [5,6]. Interestingly, one study in 2002 concluded: 'Concurrent antimicrobial administration does not alter blood culture yield' [7]. However, particularly at the time-sensitive beginning of sepsis no study

* Corresponding authors: C.S. Scheer and S.-O. Kuhn, Department of Anaesthesiology, University Hospital Greifswald, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany.
E-mail addresses: christian.scheer@uni-greifswald.de (C.S. Scheer), kuhn@uni-greifswald.de (S.-O. Kuhn).

https://doi.org/10.1016/j.cmi.2018.05.016
1198-743X/

compared blood culture results before and during antibiotic therapy. The net benefit (or harm) of blood cultures before antibiotic administration is unknown. Delayed initiation of antibiotics might be harmful. On the other hand, an immediate therapy initiation with the potential loss of pathogen detection could conflict with therapy adjustment and would strengthen the present recommendation. Therefore, timing of blood cultures seems to be of exceptional importance regarding different treatment priorities.

The present clinical cohort study was performed to analyse the impact of antibiotic administration on blood culture positivity at the beginning of sepsis.

Methods

Design and patients

This clinical cohort study was conducted at an interdisciplinary intensive care unit at the University Hospital Greifswald, Germany. Between 2010 and 2017, all consecutive adult patients with severe sepsis and septic shock and two or three sets of blood cultures at the beginning of sepsis were prospectively included.

For each patient only the first episode of sepsis was considered. Patients with blood culture sampling before antibiotic therapy were compared with those who had their blood cultures drawn during antibiotic therapy. Patients with sampling before antibiotic therapy received no antibiotics for at least 24 hours before blood culture sampling. We analysed only blood cultures obtained at the beginning of sepsis (first time when sepsis criteria were met). In accordance with the example of 'Assessment of Clinical Criteria for Sepsis' [8] we included blood culture samples obtained within 36 h before and after the beginning of sepsis.

Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria (Sepsis-1 criteria) [9] (see Supplementary material, Table S1). Medical records were reviewed to gather clinical characteristics, information about antibiotic treatment, laboratory parameters and microbiological blood culture results. Patients with missing time of blood culture sampling or unknown status of antibiotic therapy, as well as patients with only one set or more than three sets, were excluded. The local ethics committee approved the study and waived the patients' consent because of the observational character of the study (identifier: BB 133/10). The manuscript was written in accordance with the STROBE guidelines for observational studies [10].

Blood culture processing

A blood culture set comprised one anaerobic and one aerobic bottle (BACTEC™ Plus Aerobic/F and BACTEC™ Plus Anaerobic/F culture vials; Becton-Dickinson, Franklin Lakes, NJ, USA) containing resins for antibiotic neutralization. Blood cultures were obtained in accordance with current blood culture guidelines [11,12], vials were filled with 8–10 mL blood each and incubated in an automated blood culture system (BD BACTEC FX; Becton-Dickinson). Blood volume was monitored by our microbiological staff. Positive blood cultures were Gram-stained, streaked onto Columbia sheep blood agar, chocolate agar, MacConkey lactose agar and Schaedler agar (Becton-Dickinson) for overnight incubation at 37°C and species identification was then carried out using matrix-assisted laser desorption ionization time-of-flight mass spectrometry on a VITEK®MS device (bioMérieux, Marcy l'Étoile, France).

Definition of blood culture positivity and contamination

Blood culture positivity was defined as detection of a microbiological pathogen within 6 days of incubation. Blood cultures with a positive growing signal but without any microbiological pathogen identification were defined as negative. In accordance with the Q-Track study [13] we defined identification of coagulase-negative staphylococcus, *Streptococcus viridians*, *Propionibacterium acnes*, *Corynebacterium* spp. or *Bacillus* spp. in only one set of the individual sampling as suspect for contamination.

Statistical analysis

R Studio and GraphPad were used for statistical analyses. Characteristics of independent patients with sampling before and during antibiotic therapy were analysed by chi-square test, Fisher's exact test and Student's *t*-test to warrant comparability of these independent groups. Exact 95% CI were calculated by the Clopper–Pearson method. A multivariable logistic regression with odds ratios (OR) and 95% CI was performed to analyse the adjusted impact of independent predictors on blood culture positivity. A sample size calculation was not performed on account of lacking knowledge of expected differences. Furthermore, we investigated a subgroup of patients who had samples taken both before and during antibiotic therapy. Blood culture samples of these patients were analysed in a paired design. Results were rated as significant if the p value was <0.05.

Results

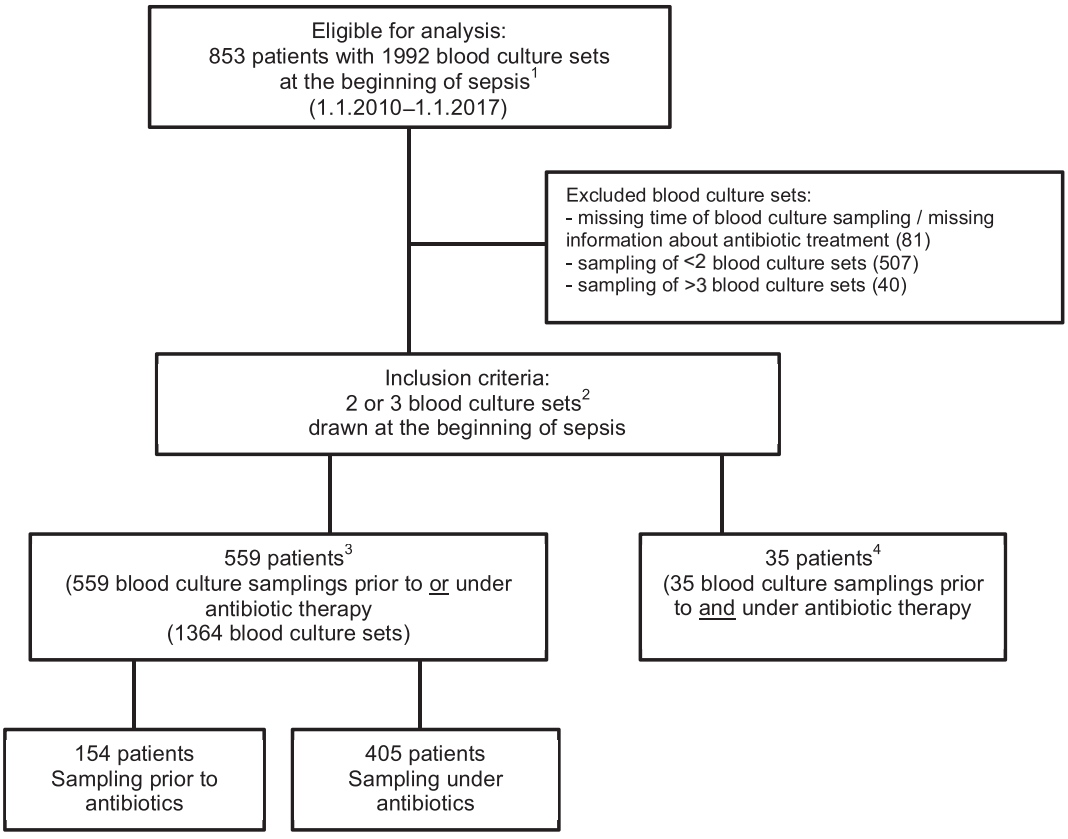
During the 7-year study period 1364 blood culture sets from 559 individuals were included. In 154 patients, blood cultures were taken before the administration of antibiotics; and in 405 patients they were taken during antibiotic therapy. Patients with fewer than two or more than three blood culture sets and missing data were excluded (Fig. 1).

Patients with sampling before antibiotics ($n = 154$) and patients with sampling during antibiotic therapy ($n = 405$) were balanced with respect to age, gender, number of obtained blood culture sets, laboratory parameters, systemic inflammatory response syndrome (SIRS) criteria, Sepsis-related organ failure assessment score (SOFA), Sepsis-1 and Sepsis-3 severity distribution, focus of infection and mortality (Table 1).

The overall positivity of all blood cultures was 34.0% (190/559). Cultures taken before antibiotic administration had a positivity of 50.6% (78/154) and those taken during antibiotic therapy had a positivity of 27.7% (112/405) (p <0.001) (Fig. 2). We found similar blood culture positivity before antibiotic therapy (48.8% (40/82) versus 51.5% (35/68), p 0.870) and during antibiotic therapy with two versus three sets of samples (27.3% (62/227) versus 29.3% (49/167), p 0.734) (Fig. 2).

Multivariable logistic regression revealed antibiotic therapy as an independent factor for less positivity (OR 0.4; 95% CI 0.3–0.6; p <0.001). Further factors of decreased positivity were septic shock and abnormalities in body temperature. Vascular devices and implants as source of infection and urogenital tract infections were factors for increased positivity (Table 2). Vascular devices and implants (66.7% (14/21); 95% CI 43.0–85.4) and urogenital tract infections (63.2% (24/38); 95% CI 46.0–78.2) were associated with the highest positivity.

A subgroup of 35 patients had both, a blood culture sample from before and also after antibiotic initiation and were analysable in a paired design. Positivity before antibiotics was 57.1% (20/35) and during antibiotics it was 25.7% (9/35) (p 0.008).



1 Patients with blood culture samplings at the beginning of sepsis (first time when Sepsis-1 criteria were met) were eligible.
2 A blood culture set contained 2 bottles, one aerobic and one anaerobic.
3 Only one sampling (2 or 3 sets) was included in each patient.
4 Patients with 2 blood culture samplings. One sampling prior to antibiotic administration and one under antibiotic therapy (before–after) within the same sepsis episode.

Fig. 1. Flow chart of analysed patients and blood culture sets.

After initiation of antibiotic therapy, 9 of the 20 initially positive tested patients remained positive. No patient with negative blood culture results before antibiotic administration became positive when on antibiotics. Mainly β-lactam antibiotics were administered (Table 3). Antibiotic regimen was adequate in 60% (111/185) of the pathogen findings under antibiotic treatment. A detailed overview of the microorganisms that grew in the blood cultures obtained before and during antibiotic therapy is presented in Table 4. Gram-positive pathogens (28.3% (111/392) versus 11.9% (116/972); p <0.001) and also Gram-negative pathogens (16.3% (64/392) versus 9.3% (90/972); p <0.001) were more frequent in blood culture sets drawn before antibiotic therapy compared with sets collected during antibiotic therapy. Contamination rates of 3.6% (14/392) and 2.4% (23/972) (p 0.220) were observed in blood culture sets before and during antibiotic therapy.

Discussion

Obtaining blood cultures during antibiotic therapy is associated with a significant loss of pathogen detection.

Culture positivity was reduced by 20% among blood cultures obtained during antibiotic therapy. The current data quantify the loss of information with blood culture sampling during antibiotic therapy and thereby, the potential loss of information required to perform a tailored antibiotic therapy. This implies major problems as antibiotic optimization and de-escalation of antibiotic therapy are substantial based on pathogen identification. The results of the unpaired analysis (patients with samples taken before antibiotics or during antibiotics) were also confirmed by the paired analysis (patients with samplings taken both before antibiotics and during antibiotics). We found a loss of pathogen detection of 30% in this subgroup.

Although our study design does not allow a definite conclusion to be drawn about the impact on patient outcome, the importance of a targeted antibiotic therapy and its effects on survival have been demonstrated in numerous trials 1 [14–16]. Furthermore, these measures counteract a selection of resistant pathogens [17–19], which also represents a serious problem in current intensive care [20].

Worldwide surveys revealed low compliance rates for blood culture samples taken before antibiotic administration [21–24]. The low level of evidence mentioned above might be responsible for these results. In addition, the comparatively good data about the importance of early, broad-spectrum antibiotics associated with mortality reduction [25–27] and prevention of shock [28] in patients with sepsis potentially contributes to a prioritization of early antibiotic administration over previous blood culture sampling.

Table 1
Characteristics of patients with blood culture samples taken at the beginning of sepsis

	Patients with BC sampling before antibiotics $n = 154$	Patients with BC sampling during antibiotics $n = 405$	p value
General characteristics *n* (%)			
Male	100 (64.9)	256 (63.2)	0.768
Female	54 (35.1)	149 (36.8)	
Age, mean (SD)	68.5 (11.2)	67.6 (12.2)	0.393
Sampling of two blood culture sets	86 (55.8)	235 (58.0)	0.702
Sampling of three blood culture sets	68 (44.2)	170 (42.0)	
Blood-culture-positive patients	78 (50.6)	112 (27.7)	<0.001
Blood-culture-negative patients	76 (49.4)	293 (72.3)	
Lactate (mmol/L), mean (SD)	4.5 (4.5)	3.9 (4.0)	0.158
Procalcitonin, mean (SD)	28.9 (60.8)	26.2 (54.0)	0.427
SOFA score,[a] mean (SD)	7.2 (3.5)	7.0 (3.4)	0.595
Sepsis severity,[b] *n* (%)			
Sepsis-1			
Severe sepsis	42 (27.5)	103 (25.5)	0.666
Septic shock	111 (72.5)	301 (74.5)	
Sepsis-3			
Sepsis	60 (39.5)	165 (40.9)	0.763
Septic shock	82 (53.9)	205 (50.9)	
No Sepsis-3	10 (6.6)	33 (8.2)	
SIRS criteria met,[b] *n* (%)			
Abnormal white-cell count	116 (81.1)	309 (81.5)	0.900
Abnormal temperature	96 (70.1)	247 (67.1)	0.592
Increased respiratory rate	30 (21.3)	123 (34.4)	0.005
Increased heart rate	131 (87.3)	336 (85.7)	0.679
Number of SIRS criteria met, mean (SD)	2.5 (0.9)	2.5 (1.0)	0.460
Focus of infection,[c] *n* (%)			
Abdominal, gastrointestinal tract	63 (41.2)	204 (50.4)	0.070
Lung, respiratory tract	34 (22.2)	91 (22.5)	
Urogenital tract	11 (7.2)	28 (6.9)	
Bone and soft-tissue	19 (12.4)	21 (5.2)	
Bacteraemia	5 (3.3)	5 (3.3)	
Vascular devices, implants	5 (3.3)	17 (4.2)	
Mixed focus[d]	7 (4.6)	19 (4.7)	
Unknown focus[e]	9 (5.9)	20 (4.9)	
Mortality, *n* (%)			
28-day	48 (32.2)	103 (26.0)	0.163
90-day	64 (44.1)	148 (38.9)	0.320

Abbreviations: BC, blood culture; SD, standard deviation.
[a] SOFA, sepsis-related organ failure assessment score; calculated without Glasgow Coma Scale.
[b] Sepsis severity and SIRS criteria are defined in the supplement.
[c] Focus of infection determined by intensive care specialists and CDC criteria.
[d] Concurrent focus of infection, meningitis, endocarditis.
[e] Source of infection was not reliable to determine; missing variables are listed in the supplement.

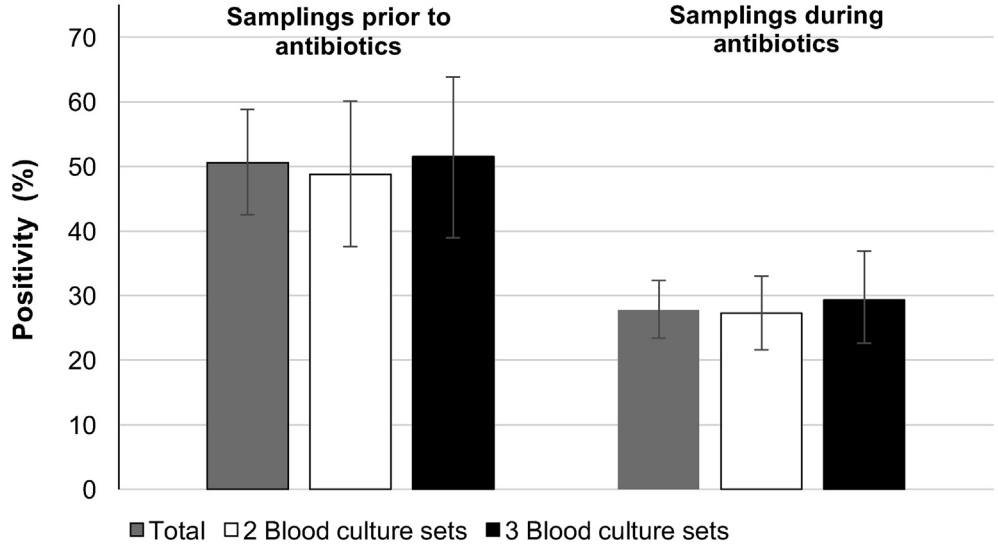


Fig. 2. Impact of antibiotic administration on blood culture positivity at the beginning of sepsis. Patients with samples taken before antibiotic administration were compared with patients with samples taken during antibiotic therapy. Pathogen discovery at the beginning of sepsis plotted as bars with 95% CI.

Table 2
Multivariable Logistic Regression (LASSO) on blood culture positivity

	Odds ratio (95% CI)	p-value
Abdominal focus of infection	Reference	
Mixed focus of infection	1.38 (0.76–2.50)	0.294
Infection of vascular devices and implants	6.08 (2.25–16.44)	<0.001
Bone and soft-tissue infections	2.05 (0.99–4.28)	0.055
Respiratory tract infections	0.74 (0.43–1.28)	0.283
Urinary tract infections	3.96 (1.88–8.33)	<0.001
Severe sepsis[b]	Reference	
Septic shock[b]	0.61 (0.38–0.97)	0.038
Sampling before antibiotic administration	Reference	
Sampling during antibiotic administration	0.38 (0.25–0.57)	<0.001
Gender male	Reference	
Gender female	0.79 (0.52–1.19)	0.254
Normal temperature	Reference	
Abnormal temperature[c]	0.62 (0.41–0.94)	0.025
Normal respiratory rate	Reference	
Respiratory rate >20/min	1.40 (0.90–2.17)	0.131
Heart rate ≤90/min	Reference	
Heart rate >90/min	1.62 (0.87–3.01)	0.131
SOFA score[a,d]	1.03 (0.96–1.10)	0.364
Lactate mmol/L (logarithmic)[e]	1.08 (0.89–1.31)	0.425

Odd ratios representing the impact of different predictors on blood culture positivity (adjusted in relation to the other influencing factors).
[a] SOFA, Sepsis-related organ failure assessment score; calculated without Glasgow Coma Scale.
[b] Sepsis severity and SIRS criteria are defined in the supplement.
[c] Hyperthermia or hypothermia.
[d] Impact of a SOFA score increase of 1 point.
[e] Impact of a doubled lactate level.

This study has limitations. First, it was performed as a single-centre study. This limits the generalizability of our findings. Second, this study analysed mainly unpaired blood cultures from different patients. However, the patients in both groups were well-balanced with regard to important characteristics, especially the distribution of two and three sets, SOFA score, sepsis severity, SIRS criteria, procalcitonin and in particular regarding the focus of infection. Furthermore, the results were validated in a small number of patients with paired blood cultures. Larger studies among patients with samples taken both before antibiotic administration and subsequently after antibiotic therapy, are needed. Third, based on the present data we cannot draw any conclusions about differences in bacterial growth times under antibiotic therapy. Fourth, conclusions about any outcome effect cannot be made from this study.

At the beginning of sepsis, obtaining blood cultures during antibiotic therapy is associated with a clinically relevant loss of pathogen identification. Blood cultures should be obtained before antibiotic administration.

Table 3
Antibiotic usage among blood culture sets drawn under antibiotic therapy

	n (%)
Blood culture sets drawn during antibiotics, total	972
Carbapenems, (e.g. meropenem, Imipenem)	530 (54.5)
Penicillin with β-lactamase inhibitor (e.g. piperacillin/tazobactam, ampicillin/sulbactam)	338 (34.8)
Other penicillins	40 (4.1)
Cephalosporins	176 (18.1)
Vancomycin, teicoplanin	85 (8.7)
Linezolid	53 (5.5)
Chinolones	101 (10.4)
Metronidazol	174 (17.9)
Clindamycin	37 (3.8)
Tigecycline	23 (2.4)
Macrolides	61 (6.3)
Other[a]	30 (3.1)

[a] For example, gentamycin, rifampicin, fosfomycin, cotrimoxazole.

Table 4
Pathogen detection among blood culture sets before and during antibiotic therapy

	Blood culture sets before antibiotic therapy (n = 392), *n* (%)	Blood culture sets during antibiotic therapy (n = 972), *n* (%)
Culture positive (microbiological pathogen finding)	153 (39.0)	185 (19.0)
Culture negative	239 (61.0)	787 (81.0)
Suspect for contamination	14 (3.6)	23 (2.4)
Gram-positive findings	111 (28.3)	116 (11.9)
Coagulase-negative staphylococcus (*Staphylococcus epidermidis*)	31 (7.9)	37 (3.8)
Staphylococcus aureus	35 (8.9)	18 (1.9)
Other staphylococci	6 (1.5)	1 (0.1)
Methicillin-resistant *S. aureus* (MRSA)	9 (2.3)	10 (1.0)
Streptococcus sp.	11 (2.8)	5 (0.5)
Enterococcus sp.	18 (4.6)	43 (4.4)
Vancomycin-resistant *Enterococcus* (VRE)	1 (0.3)	2 (0.2)
Gram-negative findings	64 (16.3)	90 (9.3)
Escherichia coli	28 (7.1)	35 (3.6)
Escherichia coli 3 MRGN	–	6 (0.6)
Proteus sp.	5 (1.3)	7 (0.7)
Serratia	1 (0.3)	2 (0.2)
Citrobacter	–	2 (0.2)
Klebsiella sp.	12 (3.1)	17 (1.7)
Klebsiella 3 MRGN	1 (0.3)	–
Pseudomonas aeruginosa	5 (1.3)	–
Stenotrophomonas	–	2 (0.2)
Clostridium sp.	2 (0.5)	17 (1.7)
Other[a]	10 (2.6)	2 (0.2)

[a] Other: Corynebacterium, Haemophilus, Bacteroides sp., Enterobacter.

Acknowledgements

We would like to express our sincere thanks towards our study-nurses Manuela Gerber and Liane Guderian, and to our medical documentalist Christian Wollmann for their indispensable help with the data collection.

Some of the preliminary data were presented at the 28th ESICM Congress in Berlin. Intensive Care Med Exp. 2015 Dec; 3(Suppl 1): A882. https://doi.org/10.1186/2197-425X-3-S1-A882. PMCID: PMC4796237.

Transparency declaration

CS reports travel reimbursement and conference expenses from Astellas pharma and lecture fees from Radiometer and Accelerate diagnostics. CF received travel fees for the DIVI congress 2015 from Astellas Pharma GmbH. MG reports grants from the Federal Ministry of Education and Research (BMBF), Germany, personal fees and non-financial support from Dräger Medical Germany, Pfizer Deutschland GmbH and Becton, Dickinson and Company. SR reported receiving travel reimbursement from Orion and Astellas, grant support from Fresenius Kabi Germany and personal fees from Amomed Pharma. SOK reports personal fees from Dräger medical Germany, Lilly medical and grants from the Federal Ministry of Education and research (BMBF) Germany. All other authors declare no conflicts of interest.

Author contributions

CS and MV performed the data analysis. CS, SR and SOK drafted the first version of the manuscript. MG, CF, JB, JAB, KZ and KH contributed to the data collection. All authors contributed to the

data interpretation. All authors amended and approved the final version of the manuscript. CS has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. CS assumes full responsibility for the integrity of the submission as a whole, from inception to published article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.05.016.

References

[1] Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 2014;40:32–40.

[2] Rhodes A, Evans L, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.

[3] Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001;108:1169–74.

[4] Zadroga R, Williams DN, Gottschall R, Hanson K, Nordberg V, Deike M, et al. Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. Clin Infect Dis 2013;56:790–7.

[5] Cardoso T, Carneiro A, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A. Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese community-acquired sepsis study (SACiUCI study). Crit Care 2010;14:R83.

[6] De Sousa AG, Fernandes Junior CJ, Santos GPD, Laselva CR, Polessi J, Lisboa LF, et al. The impact of each action in the surviving sepsis campaign measures on hospital mortality of patients with severe sepsis/septic shock. Einstein 2008;6:323–7.

[7] Schermer CR, Sanchez DP, Qualls CR, Demarest GB, Albrecht RM, Fry DE. Blood culturing practices in a trauma intensive care unit: does concurrent antibiotic use make a difference? J Trauma 2002;52:463–8.

[8] Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:762–74.

[9] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. Chest 1992;101:1644–55.

[10] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.

[11] CLSI. Principles and procedures for blood cultures; approved guideline. Wayne, PA: Clinical and Laboratory Standards Institute; 2007.

[12] Towns ML, Jarvis WR, Hsueh P. Guidelines on blood cultures. J Microbiol Immunol Infect 2010;43:347–9.

[13] Dawson S. Blood culture contaminants. J Hosp Infect 2014;87:1–10.

[14] Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31:2742–51.

[15] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237.

[16] Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Fernández-Delgado E, López-Sánchez JM. Adequate antibiotic therapy before ICU admission in patients with severe sepsis and septic shock reduces hospital mortality. Crit Care 2015;19:302.

[17] Hagel S, Pletz MW, Brunkhorst FM, Seifert H, Kern WV. Bakteriämie und Sepsis. Internist 2013;54:399–407.

[18] Kollef MH. What can be expected from antimicrobial de-escalation in the critically ill? Intensive Care Med 2014;40:92–5.

[19] Bassetti M, De Waele Jan J, Eggimann P, Garnacho-Montero J, Kahlmeter G, Menichetti F, et al. Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. Intensive Care Med 2015;41:776–95.

[20] Kollef MH, Bassetti M, Francois B, Burnham J, Dimopoulos G, Garnacho-Montero J, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. Intensive Care Med 2017;43:1187–97.

[21] Ferrer R, Artigas A, Levy MM, Blanco J, González-Díaz G, Garnacho-Montero J, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA 2008;299:2294–303.

[22] Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis*. Crit Care Med 2010;38:367–74.

[23] Phua J, Koh Y, Du B, Tang YQ, Divatia JV, Tan CC, et al. Management of severe sepsis in patients admitted to Asian intensive care units: prospective cohort study. BMJ 2011;342:d3245.

[24] Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, et al. The surviving sepsis campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). Intensive Care Med 2015;41:1620–8.

[25] Scheer CS, Fuchs C, Kuhn S, Vollmer M, Rehberg S, Friesecke S, et al. Quality improvement initiative for severe sepsis and septic shock reduces 90-day mortality. Crit Care Med 2017;45:241–52.

[26] Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749–55.

[27] Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis*. Crit Care Med 2014;42:2409–17.

[28] Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med 2017;45:623–9.