Original

Impact of a stewardship program on bacteraemia in adult inpatients

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ABSTRACT

Background. Bloodstream infections (BSIs) are associated with considerable morbidity and mortality among inpatients. The aim of this study was to evaluate the impact of a stewardship program on clinical and antimicrobial therapy-related outcomes in patients with bacteraemia.

Methods. Single-centre, before-and-after quasi-experimental study in adult inpatients. Over 1 January 2013 to 31 June 2013 all patients aged 18 years or older with a bacteraemia (intervention group, N=200) were compared to a historical cohort (1 January 2012 to 31 December 2012) (control group, N=200).

Results. Following blood culture results and adjusting for potential confounders, the stewardship program was associated with more changes to antibiotic regimens (adjusted odds ratio [ORa]: 4.6, 95% CI 2.9, 7.4), more adjustments to antimicrobial therapy (ORa: 2.4, 95% CI 1.5, 3.8), and better source control in the first five days (ORa 1.6, 95% CI: 1.0, 2.7). In the subgroup that initially received inappropriate empiric treatment (n=138), the intervention was associated with more antibiotic changes (OR: 3.9, 95% CI: 1.8, 8.5) and a better choice of definitive antimicrobial therapy (OR 2.3 95% CI: 1.2, 4.6). There were also more antibiotic changes in the subgroups with both Gram-negative (OR: 2.8, 95% CI: 1.6, 4.9; n=217) and Gram-positive (OR: 4.6, 95% CI: 1.8, 9.9; n=135) bacteraemia among those receiving the intervention, while the Gram-positive subgroup also received more appropriate definitive antimicrobial therapy (OR: 3.9, 95% CI: 1.8, 8.8).

Conclusion: The stewardship program improved treatment of patients with bacteraemia and appropriateness of therapy.

Key words: Stewardship, Bacteraemia; Anti-bacterial agents; Therapeutic use; Gram-negative bacterial infections; Gram-positive bacterial infections; Hospitalization.

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Impacto del programa de intervención en bacteriemia en pacientes adultos

RESUMEN

Introducción. Las bacteriemias están asociadas con una elevada morbilidad y mortalidad en pacientes hospitalizados. El objetivo del estudio fue evaluar el impacto de un programa de intervención clínica y de terapia antimicrobiana en pacientes con bacteriemia.

Material. Estudio en un centro tipo cuasi-experimental pre y post-intervención en pacientes adultos hospitalizados. Desde 1 enero 2013 a 31 junio 2013, todos los pacientes mayores de 18 años en los que se identificaba una bacteriemia (grupo de intervención) se compararon con una cohorte histórica de bacteriemia (1 enero 2012 a 31 diciembre 2012) (grupo control).

Resultados. Se incluyeron 200 pacientes en cada grupo. Después de ajustar por los posibles factores de confusión y tras conocer el resultado de los hemocultivos, el grupo de intervención tuvo más cambios de antibióticos (Odds ratio ajustada [ORa]: 4,6, intervalo de confianza [IC] 95%: 2,9-7,4), mayor adecuación del tratamiento antibiótico (ORa: 2,4, IC 95%: 1,5-3,8) y mayor control de la infección en los primeros cinco días (ORa 1,6, IC 95%: 1,0-2,7). En el subgrupo de pacientes que seguían un tratamiento inadecuado cuando se identificó el microorganismo en el hemocultivo (n =138), la intervención se asoció con un mayor cambio de antibiótico (OR: 3,9, IC 95%: 1,8-8,5) y una mejor elección final del antibiótico (OR: 2.3; IC 95%: 1.2-4.6). En el subgrupo de bacteriemia por gramnegativos (n=217), el programa de intervención en bacteriemia se asoció con un mayor cambio de antibiótico (OR: 2,8; IC 95%: 1,6-4,9) y en el subgrupo de bacteriemia por microorganismos grampositivos (n=135), el programa de intervención indujo un mayor cambio en el uso de antibióticos (OR: 4,6, IC 95%: 1,8-9,9) y una mejor elección final del tratamiento (OR: 3,9; 95% CI: 1,8-8,8).

Conclusión. El programa de intervención en bacteriemia mejoró el tratamiento de los pacientes con bacteriemia y la adecuación del mismo.

Palabras clave: Programa de control; bacteriemia; agentes antibacterianos, terapéutica, infecciones por gramnegativas, infección por gramnegativos, hospitalización

INTRODUCTION

Bloodstream infections (BSI) are associated with considerable levels of morbidity and mortality among inpatients despite improvements in antimicrobial therapy and supportive care[1]. Rapid identification of the pathogen is essential for choosing an appropriate antimicrobial therapy, while prompt initiation of treatment can improve patient outcomes and decrease healthcare expenditures[2-4]. In contrast, delays in microbiological diagnosis undermine clinicians' capacity to choose the best treatment, needlessly exposing patients to broad-spectrum antimicrobials that increase the risk of antibiotic resistance in different isolates[5].

In this context, antimicrobial stewardship programs (SPs) incorporating real-time review and intervention can improve patient outcomes compared to simple reporting of microbiology results[6-10]. The aim of this study was to evaluate the impact of an SP on clinical and antimicrobial therapy-related outcomes in patients with BSIs.

METHODS

Study design and setting. This was a single-centre, before-and-after quasi-experimental study in adult inpatients with bacteraemia. The study took place at the Hospital General Universitario de Alicante (HGUA), a tertiary, 755-bed acute care teaching hospital in Alicante (Spain), covering a population of 274,271 inhabitants. The hospital has all medical and surgical specialties and is a referral centre for a portion of Alicante province (pop. 1.9 million) in certain surgical (vascular, thoracic, cardiac, and plastic surgery) and medical (clinical haematology, endocrinology) specialties. In 2013 there were a total of 30,838 admission, 141,246 emergencies, 21,178 surgical interventions and 193,045 stays (mean: 6.26 days). Average occupancy rate was 70.04%, with a rotation index of 40.84.

Participants. All adult inpatients (aged ≥18 years) with BSI, identified by both traditional microbiological techniques (Gram, culture and antibiogram by micro dilution; Walk Away, Beckman, USA) and new techniques (MALDI-TOF; Bruker, Germany) from a blood culture, with rapid detection of methicillin-resistant *Staphylococcus aureus* using GeneXpert (Cepheid, USA). We compared BSI cases diagnosed from 1 January 2013 to 31 June 2013 (intervention group following implementation of the antimicrobial SP) versus a random sample of a historical cohort (1 January 2012 to 31 December 2012) (control group). We excluded patients with an active BSI transferred from another hospital and those in the Intensive Care Unit and the Infectious Disease Unit. Additional exclusion criteria were BSI due to contaminant microorganism, death in the first 24 hours, and transfer to another centre without clinic follow-up (figure 1). We choose 200 episodes during intervention group and other 200 episodes from historical cohort as control group (with randomized exclusion from all BSI). All participants in the intervention group gave their informed consent. Informed consent was not required from the control group due to the retrospective nature of this study arm. The institutional review board of the hospital approved the study.

Pre-intervention period (control group). Attending physicians were notified of positive Gram stain results from blood cultures and they carried out the clinical evaluation of the patient, the diagnostic process and the determination of the antimicrobial therapy. Consultation to the Infectious Diseases Unit only occurred upon explicit request from the attending physician.

We collected variables related to the episodes of bacteraemia during this control period (clinical, microbiological, treatment and outcome data) from a retrospective database.

Intervention group (stewardship program). In January 2013, an SP was launched at the HGUA, involving two infectious diseases physicians, two infectious disease pharmacists, two microbiologists and two preventive medicine physicians. One of their functions was an intervention on bacteraemia. An SP member from the Microbiology Unit communicated in real time for all adult patients with positive blood cultures of bacteria and yeast. An SP member from the Infectious Diseases Unit received the information, then performed a clinical evaluation of the patient, contacting the attending physician and providing recommendations for diagnostic evaluation and antimicrobial therapy according to the evidence-based institutional guidelines. These recommendations were updated as the results of the Gram stain; organism identification and antimicrobial susceptibility testing became available. Acceptance of these recommendations by the patient's attending physician was verified at 24–48 hours, and if this was granted, the patient was clinically monitored until resolution of the infectious process. For each episode of BSI, investigators collected microbiological, treatment and outcome variables during hospitalization and up to 60 days after discharge on a data collection sheet.

Outcomes. We measured definitive effective and optimal antimicrobial therapy, changes of treatment after results of BSI, time on infectious focus in the first five days of the intervention, cure of BSI, 30-day all-cause mortality, recurrence of same BSI and length of hospitalization > 10 days.

Data collection. We collected demographic and clinical data from medical records and stored them in a database, including *patient identification data*: age, sex, unit of admission, and date of entry; *microbiological variables*: date of blood culture, number of positive cultures, rise time, resistance profile, and date of any subsequent blood cultures; *clinical variables*: principal diagnosis, comorbidity, immunosuppression (corticosteroids, chemotherapy, immunosuppressive disease, presence of prosthesis or endovascular catheterization); *bacteraemia variables*: community, health-related

or nosocomial bacteraemia and origin; *treatment variables*: empiric treatment (indication and dosing), targeted therapy, duration, relevant toxicity, source control (catheter removal, surgery or percutaneous drainage); and *evolution variables*: clinical outcomes, complications, length of hospital stay, readmission due to bacteraemia, mortality during admission and at three months.

Definitions. When coagulase-negative *Staphylococcus* (CoNS) or other skin flora microorganisms were recovered from one out of two or more sets of collected blood cultures, we deemed these to be contaminant, except for patients with suspected infection of central venous catheters or surgically implanted prosthetic material.

We considered appropriate empiric antibiotic therapy to be prompt administration (≤24 h of index blood culture sampling) of an antimicrobial agent to which the isolate was susceptible on the final susceptibility report. We based susceptibility interpretations on the published Clinical and Laboratory Standards Institute cutoffs for that period, as reported by the microbiology laboratory. Selection of antimicrobial therapy was at the discretion of the attending physician.

Definitive effective and optimal antimicrobial therapy was assessed. We considered *effective* definitive therapy to be when the microorganism was susceptible to treatment according to final susceptibility report. *Optimal* definitive therapy was defined as the antibiotic of choice for the isolated microorganism on the final report.

We considered length of stay to begin following blood culture positivity for BSI and excluded from our analysis patients who died in the hospital. We defined infection-related mortality according to the attending physician's criteria.

For patients in whom pathogen(s) not included in evidence-based guidelines were identified, an infectious diseases specialist of SP decided on the most appropriate empiric therapy. We classified interventions as (a) broadening or initiating coverage, (b) narrowing antimicrobial coverage to target the isolated organism, (c) discontinuing therapy or (d) other.

The SP team recorded all recommended interventions and prescriber acceptance rates, as well as the timing of the intervention in relation to Gram stain, organism identification, and antimicrobial susceptibilities during the intervention period.

Statistical analysis. We performed all statistical analyses using SPSS software, version 22.0 (SPSS, Inc, Chicago, Illinois). Demographic data were analyzed using descriptive statistics; outcomes with categorical data, by the U-Mann Whitney test; and outcomes with dichotomous data, by Pearson's χ^2 test. We adjusted outcome variables for potential confounders, selected based on significant ($P < 0.05$) differences between groups on the bivariate model, and we used the adjusted odds ratio (ORa) to measure association. After that, we conducted a stratified analysis to assess clinical outcomes in patients with Gram-positive and Gram-negative organisms and in those receiving inappropriate empiric antibiotic treatments. We used the OR to measure association.

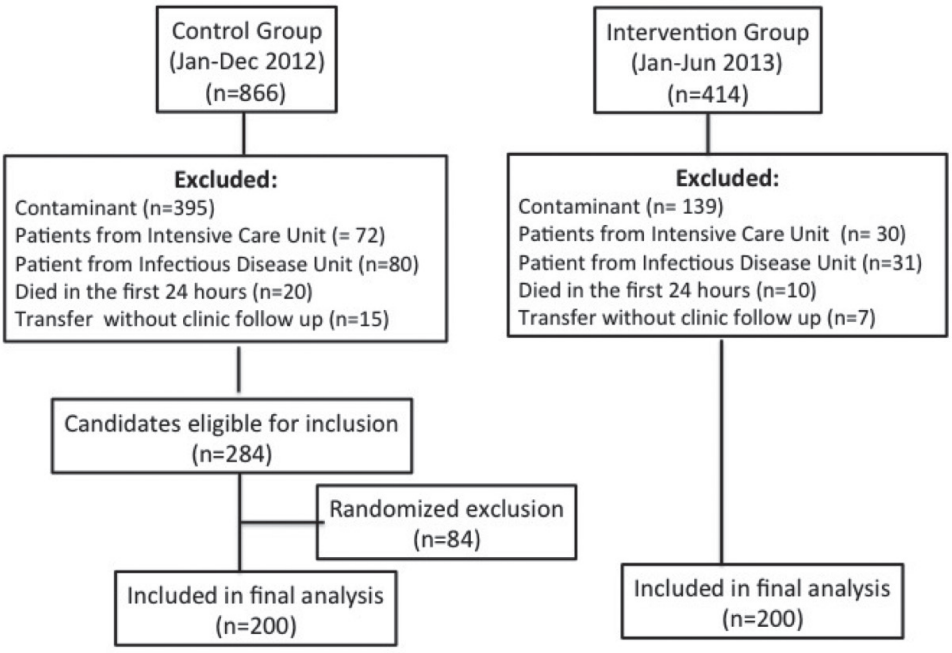

Figure 1 | **Flowchart of study participants**

Table 1 Participant characteristics

Baseline demographics	Intervention group (N=200)	Control group (N=200)	p-value
Sex, male	115 (57.5)	113 (56.5)	0.840
Mean age ± SD (years)	66.6 ± 17.0	66.7 ± 17.2	0. 961
Surgical admission	49 (24.5)	32 (16.0)	**0.023**
Type of acquisition			0.864
Community acquired	90 (45)	90 (45)	0.995
Health care	51 (25.5)	55 (27.5)	0.864
Hospital acquired	59 (29.5)	55 (27.5)	0.731
Immunosuppression	114 (57)	114 (57)	0.540
Charlson Index >=3	104 (52)	82 (41)	**0.018**
McCabe Index, mean ± SD	2.3 ± 0.7	2.3 ± 0.8	0.932
Comorbidities	124 (62)	129 (64.5)	0.339
Central venous catheter	54 (27)	56 (28)	0.455
Nasogastric tube	6 (3%)	8 (4%)	0.393
Urinary catheterization	43 (21.5)	34 (17)	0.155
Mechanical ventilation	17 (8.5)	3 (1.5)	**0.001**
Surgery previous	17 (8.5)	2 (1.5)	**0.001**
Antibiotic therapy previous	74 (37)	92 (46)	**0.042**
Septic shock	66 (33)	46 (23)	**0.017**
Origin of the infection			0.273
Genitourinary	53 (26.5)	60 (30)	0.438
Respiratory	22 (11)	31 (15.5)	0.412
Foreign device	46 (23)	33 (16.5)	0.102
Skin and soft tissue infection	15 (7.5)	11 (5.5)	0.873
Intra-abdominal	52 (26)	58 (29)	0.523
Other	12 (6)	7 (3.5)	0.723
Organism distribution			
Gram-negative organisms	97 (48.5)	120 (60)	**0.020**
Gram-positive organisms	76 (38)	59 (29.5)	0.073
Yeast	9 (4.5)	3 (1.5)	0.139
Poly-microbial cultures	18 (9)	18 (9)	0.995
Microorganism resistant	26 (13)	29 (14.5)	0.386
Inadequate empiric antibiotic treatment	73 (36.5)	65 (32.5)	0.231

Notes: data are n (%), unless otherwise stated. SD: standard deviation

RESULTS

A total of 400 patients with positive blood cultures were included, 200 in each group (figure 1).

Comparison of epidemiological characteristics. There were no differences between groups in sex, mean age, McCabe index, immunosuppression factors, central venous catheter, urinary catheter or previous surgery (table 1). The patients in the intervention group had a higher Charlson Index, more bacteraemia from surgical services, more mechanical ventilation, more previous surgery and more sepsis/septic shock, while Gram-negative aetiology was less frequent. The inappropriateness of empiric treatment was similar in both groups (32% vs 35%).

After controlling for potential confounders (variables with p value <0.05 in between-group comparison), the intervention group was independently associated with antibiotic change following blood cultures (ORa: 4.6, 95% CI 2.9, 7.4), appropriate choice of definitive treatment (ORa: 2.4, 95% CI 1.5, 3.8) and early source control (< 5 days) (ORa: 1.6, 95% CI 1.0, 2.7) (table 2). Carbapenems were changed in 79% and glycopeptides in 86% of the intervention group. We did not observe differences in mortality, complications (at 30 or 60 days) or length of stay between groups.

In the subgroup that initially received inappropriate empiric treatment (n=138), the SP was associated with more antibiotic change following BSI results (82.2% vs. 53.8%; OR: 3.9; p < 0.001) and higher final optimal antimicrobial therapy (72.6 vs. 53.8%; OR: 2.3; p = 0.022). The intervention was also associated with more antibiotic changes in the subgroups with both Gram-negative (61.5% vs. 35.8%; OR: 2.8; p < 0.001) and Gram-positive (84.2% vs. 57%; OR: 4.6; p < 0.001; n = 135) bacteraemia, while the Gram-positive subgroup also received more appropriate final antimicrobial therapy (81.6% vs. 49.2%; OR: 3.9; p < 0.001) (table 3).

DISCUSSION

We report the implementation of an SP at a 700-bed university-affiliated teaching hospital in the first 200 BSI cases attended. Different studies have recommended using changes in antimicrobial resistance patterns associated with antimicrobial SP as a potential outcome measure for program assistance of bacteraemia[11,12]. In our study the SP was associated with 4.6 times better odds of antibiotic change

Table 2 **Clinical and treatment-related outcomes of participants in stewardship program (intervention group) and control group.**

	Intervention group	Control group	P-value	Adjusted OR* (95% CI)	Adjusted p-value
Effective definitive antimicrobial therapy	184 (92)	182 (91)	0.72	1.33 (0.62, 2.85)	0.46
Optimal definitive antimicrobial therapy	151 (75.5)	116 (58)	<0.001	2.41 (1.52, 3.83)	<0.001
Antibiotic changes following BSI results	145 (72.9)	80 (40)	<0.001	4.62 (2.89, 7.39)	<0.001
Infection focus < 5 days	64 (32)	40 (20)	0.006	1.65 (1.01, 2.76)	0.046
Cure of BSI	174 (87)	174 (87)	0.998	1.24 (0.64, 2.40)	0.51
30-day all-cause mortality	42 (21)	41 (20.5)	0.998	0.85 (0.49, 1.47)	0.58
Recurrence of same BSI	3 (1.5)	2 (1.0)	0.921	1.21 (0.44, 1.67)	0.82
Length of hospitalization[a] > 10 days	85 (42.5)	86 (43)	0.919	1.08 (0.70, 1.65)	0.72

Notes: data are n (%). BSI: bloodstream infection, OR: odds ratio; CI: confidence interval.

[a]Length of hospitalization was defined as time from blood culture positivity to discharge.

***Odds ratio (OR) adjusted for: surgical admission, Charlson Index ≥ 2, mechanical ventilation, antibiotic therapy previous ventilation, surgery previous, gram-negative organism**

after the results of BSI, 2.4 times better odds of receiving optimal antimicrobial therapy, and 1.7 times the odds that the infection focus lasted under five days post-intervention. Moreover, in all subgroup analyses performed, we observed a significant increase in antibiotic changes and in administration of optimal definitive antimicrobial therapy in patients receiving the intervention.

These data are also consistent with a recent systematic review and meta-analysis assessing the effects of rapid pathogen identification (MALDI-TOF) plus SP for managing BSI[13]. The availability of real-time information, framed within an active SP, can reduce time to appropriate therapy and the length of hospital stay[13,14]. On the other hand, in our study the average stay did not decrease with the SP, unlike in other studies analyzing stewardship programs in the United States [3,4].

The literature also contains examples of other studies where SPs have decreased inappropriate antimicrobial prescribing in Gram-positive bacteraemia, especially—as in our study—CoNS. Nagel and colleagues found a decreased need for additional vancomycin therapeutic drug monitoring in people with blood cultures contaminated by CoNS[15]. We did not measure this variable, having excluded the bacteraemia where CoNS could be a blood culture contaminant. However, although our SP was not designed for this purpose, we are seeing a decrease of inappropriate antimicrobial treatment following the intervention.

As this study reports only on the first months of the antimicrobial SP, it was not possible to assess the potential impact of the intervention on the resistance rates of *P. aeruginosa* to carbapenems, ciprofloxacin and amikacin, or the contribution to decreasing the detection rate of methicillin-resistant *Staphylococcus aureus* or *Clostridium difficile* colitis, as in others studies[9,16,17]. Other authors have also reported a decrease in adverse reactions to antimicrobials[16,17].

Data from a large set of studies show that inappropriate antibiotic treatment carries numerous risks, including an increased risk of hospital mortality[10]. Although we did not detect any reduction in recurrence or mortality due to bacteraemia, this may be attributable in part to our exclusion of patients admitted in the intensive care unit and to the common use of empiric treatment with broad-spectrum drugs. Indeed, using infection-related mortality indicators in infectious diseases is controversial, as cases of death are often multifactorial, which hinders accurate estimation[18]. In any case, it is crucial to couple broad-spectrum empiric antimicrobial therapy with similar de-escalation and duration of therapy processes in order to limit the emergence of antimicrobial resistance[19,20].

This study has several limitations. The study design was not a randomized controlled study but a quasi-experimental before-and-after study. Moreover, we did not assess the cost effectiveness of the intervention[21,22], although several studies have found cost reductions after implementing antimicrobial SPs, with long-term cost savings compared to traditional approaches[9,16,23], even after a 7-year period[16]. From the hospital perspective, these interventions are also cost effective[3].

This pilot study showed that the SP recommendations for non-critically ill adult inpatients with BSI had good acceptability, especially regarding drug treatment. This is consistent with the acceptance of multidisciplinary infectious diseases teams seen elsewhere[8]. Other potential advantages of a multidisciplinary infectious disease team approach (not covered here) include better management of patients with suspected or diagnosed invasive fungal diseases or associated BSI[24,25].

The SP had a positive impact on both management and clinical outcomes in patients with BSI, resulting in more rapid control of the source of bacteraemia, improved treatment (adequacy of treatment), and better use of antibiotics. We encourage the expansion of antimicrobial stewardship initiatives to improve patient outcomes, facilitate adherence to quality assurance measures, promote comprehensive disease management, and ensure appropriate use of antimicrobial agents.

Table 3 **Clinical and treatment-related subgroup outcomes: inadequate empiric antimicrobial treatment, bloodstream infections (BSI) due to Gram-negative and Gram-positive organisms.**

Outcome	Inadequate empiric antibiotic treatment (n=138)				Gram-negative organisms (n=217)				Gram-positive organisms (n=135)			
	Intervention group (n=73)	Control group (n=65)	P-value	OR (95% CI)	Intervention group (n=97)	Control group (n=120)	P-value	OR (95% CI)	Intervention group (n=76)	Control group (n=59)	P-value	OR (95% CI)
Effective definitive antimicrobial therapy	62 (84.9)	49 (75.4)	0.158	1.84 (0.78, 4.32)	87 (89.7)	112 (93.3)	0.333	0.62 (0.23, 1.64)	72 (94.7)	55 (93.2)	0.71	1.30 (0.33, 5.4)
Optimal definitive antimicrobial therapy	54 (72.6)	35 (53.8)	**0.022**	2.27 (1.18, 4.61)	64 (66)	73 (60.8)	0.435	1.24 (0.72, 2.18)	64 (84.2)	34 (57.0)	**<0.001**	3.92 (1.75, 8.76)
Antibiotic changes following BSI results	60 (82.2)	35 (53.8)	**<0.001**	3.95 (1.82, 8.50)	59 (61.5)	43 (35.8)	**<0.001**	2.85 (1.63, 4.95)	62 (81.6)	29 (49.2)	**<0.001**	4.58 (1.75, 9.92)
Infection focus < 5 days	22 (30.1)	16 (24.6)	0.479	1.32 (0.20, 2.80)	28 (28.9)	22 (18.3)	0.067	1.80 (0.71, 3.42)	27 (35.5)	13 (22)	0.089	1.95 (0.89, 4.23)
Cure of BSI	60 (82.2)	56 (86.6)	0.526	0.74 (0.29, 1.87)	90 (92.8)	105 (87.5)	0.20	1.83 (0.71, 4.70)	65 (85.5)	51 (86.4)	0.88	0.92 (0.35, 2.47)
30-day all-cause mortality	20 (27.4)	13 (20)	0.309	1.50 (0.68, 3.34)	18 (18.0)	23 (19.2)	0.90	0.96 (0.48, 1.90)	15 (19.7)	12 (20.3)	0.93	0.96 (0.41, 2.25)
Length of hospitalization[a] > 10 days	35 (47.9)	36 (55.4)	0.383	0.74 (0.37, 1.45)	58 (39.2)	57 (47.5)	0.219	0.71 (0.41, 1.22)	36 (47.7)	20 (33.9)	0.11	1.75 (0.86, 3.54)

Notes: data are n (%). OR: odds ratio; CI: confidence interval.

[a]Length of hospital stay was defined as time from blood culture positivity to discharge.

CONFLICT OF INTEREST

None to declare

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