IJID Regions 6 (2023) 167–170

Contents lists available at ScienceDirect

IJID Regions

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

Retrospective analysis of bacteraemia due to extended-spectrum beta-lactamase-producing Enterobacterales: the challenge of healthcare-associated infections

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ARTICLE INFO

Keywords:
Healthcare-associated infections
Extended-spectrum beta-lactamases
Bacteraemia
Sepsis
Antimicrobial resistance

ABSTRACT

Objectives: Healthcare-associated bacteraemia is defined as bacteraemia diagnosed ≤48 h after hospital admission in patients recently exposed to healthcare procedures or settings. It differs from hospital-acquired bacteraemia, which is diagnosed >48 h after hospital admission. Healthcare-associated bacteraemia is reported increasingly, often due to resistant pathogens including extended-spectrum beta-lactamase (ESBL) producers, representing a challenge to empirical treatment. This study aimed to assess the appropriateness of empirical treatment for ESBL bacteraemia at the authors' centre, to perform a descriptive analysis according to the mode of infection acquisition (community-acquired, healthcare-associated, hospital-acquired), and to assess the risk factors for mortality.
Methods: A retrospective study on patients with ESBL bacteraemia was undertaken.
Results: In total, 129 consecutive cases of bacteraemia due to ESBL producers were included in this study. Compared with community- and hospital-acquired bacteraemia, healthcare-associated bacteraemia affected older patients (P=0.001) and patients with higher Charlson Comorbidity Index scores (P=0.007), and was more frequently associated with piperacillin-tazobactam resistance (P=0.025) and multi-drug resistance (P=0.026). Overall, ineffective empirical treatment was common (42%). Factors associated with 30-day mortality were septic shock [odds ratio (OR) 7.096, 95% confidence interval (CI) 2.58–24.58], high Pitt score (OR 6.636, 95% CI 1.71–23.62) and unknown source of bacteraemia (OR 19.28, 95% CI 2.80–30.70).
Conclusions: Antimicrobial stewardship interventions focusing on both in-hospital and community settings are advocated to better manage healthcare-associated infections due to ESBL producers.

Background

Due to increasing medicalization and prolonged life expectancy in high-income countries, healthcare-associated infections are reported increasingly. These were originally defined by Friedman et al. as infections occurring ≤48 h after hospital admission in patients who had received recent intravenous therapy, wound or nursing care, haemodialysis or chemotherapy, or were recently hospitalized or resided in long-term care facilities. Healthcare-associated infections differ from hospital- and community-acquired infections, which are diagnosed >48 h after hospital admission, and ≤48 h after hospital admission in patients without risk factors for healthcare-associated infections, respectively [1].

Significantly, while stratifying the likelihood of multi-drug-resistant aetiologies in hospital- and community-acquired infections can be quite straightforward, healthcare-associated infections are often overlooked.

Despite mixed results, some studies have suggested that healthcare-associated infections due to extended-spectrum beta-lactamase (ESBL) producers may be higher risk for inactive empirical treatment and adverse outcomes compared with hospital- and community-acquired infections [2,3], highlighting the need to improve the management of affected patients.

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https://doi.org/10.1016/j.ijregi.2023.01.005
Received 9 August 2022; Received in revised form 10 January 2023; Accepted 11 January 2023

Table 1
Patients' demographic and clinical characteristics according to mode of bacteraemia acquisition

	Total[c] (*n*=129)	Community-acquired (*n*=36)[c]	Healthcare-associated (*n*=58)[c]	Hospital-acquired (*n*=35)[c]	*P*-value[d]
Age (years), mean, median (Q1–Q3)	72.9, 77.0 (64.0–84.0)	73.4, 77.0 (69.5–82.5)	77.2, 79.5 (67.0–86.0)	65.3, 65.0 (55.0–81.0)	0.001
Female	59 (45.7)	17 (47.2)	28 (48.3)	14 (40.0)	NS
Charlson Comorbidity Index, mean, median (Q1–Q3)	6.4, 7.0 (4.0–8.0)	5.8, 6.0 (3.5–8.5)	7.3, 7.0 (6.0–9.0)	5.4, 5.0 (3.0–8.0)	0.007
Any antibiotic in previous 30 days	71 (55.0)	10 (27.8)	34 (58.6)	27 (77.1)	0.0001
Bacteremia source					0.0002
Urinary	68 (52.7)	24 (66.7)	37 (63.8)	7 (20.0)	
Other	27 (20.9)	7 (19.4)	8 (13.8)	12 (34.3)	
Unknown	34 (26.4)	5 (13.9)	13 (22.4)	16 (45.7)	
Bacteria					NS
Escherichia coli	115 (89.1)	31 (86.1)	54 (93.1)	30 (85.7)	
Klebsiella spp.	14 (10.9)	5 (13.9)	4 (6.9)	5 (14.3)	
Presentation with septic shock	25 (19.4)	7 (19.4)	8 (13.8)	10 (28.6)	NS
Pitt score					NS
0–1	69 (53.5)	17 (47.2)	33 (56.9)	19 (54.3)	
2–6	58 (45.0)	18 (50.0)	25 (43.1)	15 (42.9)	
ICU admission	10 (7.8)	1 (2.8)	1 (1.7)	8 (22.9)	0.0012
Empirical treatment					NS
Piperacillin-tazobactam[a]	48 (37.2)	15 (41.7)	22 (37.9)	11 (31.4)	
Meropenem	29 (22.5)	7 (19.4)	12 (20.7)	10 (28.6)	
Other[b]	44 (34.1)	14 (38.9)	22 (37.9)	8 (22.9)	
Ineffective empirical treatment	54 (41.9)	18 (50.0)	30 (51.7)	6 (17.1)	0.001
Definitive treatment					0.019
Piperacillin-tazobactam[a]	36 (27.9)	14 (38.9)	11 (19.0)	11 (31.4)	
Meropenem	84 (65.1)	21 (58.3)	44 (75.9)	19 (54.3)	
Other	8 (6.2)	0	3 (5.2)	5 (14.3)	
Unknown	1 (0.8)	1 (2.8)	0	0	
Antimicrobial resistance					
Piperacillin-tazobactam	33 (25.6)	8 (22.2)	21 (36.2)	4 (11.4)	0.025
Fluoroquinolones	119 (92.2)	34 (94.4)	53 (91.4)	32 (91.4)	NS
Amikacin	4 (3.1)	1 (2.8)	3 (5.2)	.	NS
Gentamicin	54 (41.9)	17 (47.2)	28 (48.3)	9 (25.7)	NS
Resistance to multiple antibiotics					0.026
0	3 (2.3)	0	3 (5.2)	0	
1	30 (23.3)	10 (27.8)	7 (12.1)	13 (37.1)	
2	48 (37.2)	14 (38.9)	20 (34.5)	14 (40.0)	
≥3	48 (37.2)	12 (33.3)	28 (48.3)	8 (22.9)	

ICU, intensive care unit; NS, not significant.
[a] Including monotherapy and combination treatment with aminoglycosides and fluoroquinolones.
[b] Including third-generation cephalosporin, aminoglycosides and fluoroquinolones as monotherapy and in combination.
[c] Data are presented as frequency and percentage unless specified as mean, median and interquartile range (Q1–Q3) depending on factor distribution.
[d] Chi-squared test or Fisher's exact test for discrete variables, and analysis of variance or Kruskal–Wallis test for continuous variables.

Methods

This retrospective study included patients with bactaeremia due to ESBL-producing *Escherichia coli* or *Klebsiella* spp. between 2015 and 2016 at San Gerardo Hospital, Monza, Italy. The aim of this study was to assess the appropriateness of empirical therapy, perform a descriptive analysis according to the mode of infection acquisition, and assess factors associated with mortality.

The original definition by Friedman et al. was used to classify the mode of infection acquisition [1]. Hospital-acquired bacteraemia was defined as bacteraemia that occurred >48 h after hospital admission. Healthcare-associated bacteraemia was defined as bacteraemia that occurred ≤48 h after hospital admission in patients who met any of the following criteria: received intravenous therapy at home, wound care or specialized nursing care in the previous 30 days; received haemodialysis or intravenous chemotherapy in the previous 30 days; were hospitalized for ≥2 days in the previous 90 days; and resided in a nursing home or long-term care facility. Community-acquired bacteraemia was defined as bacteraemia that occurred ≤48 h after hospital admission in patients without risk factors for healthcare-associated infection [1].

Empirical treatment was classifed as effective if at least one antimicrobial active against the bacterial isolate was commenced before blood culture results were available. Empirical treatment was classifed as ineffective if this condition was not met.

Categorical variables are presented as frequency and proportion, and continuous variables are presented as median and interquartile range. Chi-squared test or Fisher's exact test was used to compare categorical variables, and analysis of variance or Kruskal-Wallis test was used to compare continuous variables. Associations between factors and in-hospital mortality, and mortality within 7 and 30 days of infection onset were assessed using logistic regression models and odds ratio (OR) estimates considering age as a potential confounder. More complex multi-variable models were not considered due to the low number of events, except for the source of infection, for which clinical severity was also considered as a confounder (defined based on the presence of at least one of the following: septic shock, intensive care unit admission, use of inotropic agents, mechanical ventilation, cardiac arrest in the prior 24 h). Kaplan–Meier curves for 30-day mortality, overall and according to the variables of interest, were plotted. Bonferroni's correction was used to adjust *P*-values when the association between comorbidities and the three modes of infection acquisition were analysed without pre-planned hypotheses. Analysis was undertaken using SAS 9.4 (SAS Inc., Cary, NC, USA).

Results

In total, 129 patients with ESBL-producing *E. coli* and *Klebsiella* spp. bacteraemia were included in the study. Table 1 summarizes the patient characteristics.

Significantly, although >92% of patients received empirical treatment with anti-Gram-negative antimicrobials, up to 41.9% received ineffective empirical treatment, mainly due to the high rates of antimicrobial resistance shown by the isolates. The highest resistance rate was found for fluoroquinolones (92.2%).

Overall, 58/129 bacteraemias were healthcare-associated, 36 were community-acquired and 35 were hospital-acquired. Descriptive analysis according to mode of acquisition showed some differences between groups (Table 1). Specifically, patients with healthcare-associated bacteraemia were older (P=0.001) and had higher Charlson Comorbidity Index scores compared with patients with community- and hospital-acquired bacteraemia (P=0.007). Patients with community-acquired and healthcare-associated bacteraemia were more likely to have a urinary source of infection, while patients with hospital-acquired bacteraemia were more likely to have an unknown source of infection (P=0.0002) and required ICU admission more frequently (P=0.0012).

Ineffective empirical treatment was more common in healthcare-associated and community-acquired bacteraemia compared with hospital-acquired bacteraemia (P=0.011). Isolates from healthcare-associated infections were more likely to show resistance to piperacillin-tazobactam (P=0.025) and to have a multi-drug-resistant phenotype (P=0.026), and were consequently more likely to be treated with carbapenems as definitive treatment (P=0.02).

In-hospital mortality was 14% [95% confidence interval (CI) 9.1–22.0], with 16 and 13 of the 19 deaths occurring within 30 and 7 days of infection onset, respectively (Table S1, see online supplementary material). Table S2 (see online supplementary material) shows the distribution of selected variables according to survival status 30 days after infection onset. Factors associated with 30-day mortality according to logistic regression after adjusting for age were septic shock (OR 7.96, 95% CI 2.58–24.58) and high Pitt score (≥2) (OR 6.36, 95% CI 1.71–23.62). Unknown source of bacteraemia was confirmed to be associated with mortality after adjusting for clinical severity and age (OR 6.85, 95% CI 1.97–23.87). Comparable results were obtained considering in-hospital and 7-day mortality. Kaplan–Meier curves for 30-day mortality, overall and according to the variables of interest, are shown in Figure S1 (see online supplementary material).

Discussion

The study data highlight the significance of bacteraemia due to ESBL-producing Enterobacterales in terms of morbidity, prevalence of co-resistance, and treatment challenges.

Specifically, it is of concern that, despite the prompt introduction of empirical therapy covering Gram-negative pathogens in most cases of suspected bacteraemia, up to 42% of patients received an ineffective empirical treatment, mainly due to the high prevalence of resistance. In agreement with another study from Italy [3], inactive empirical treatment was common in healthcare-associated infections, which represented the most common type of bacteraemia according to mode of infection acquisition in the present study. Ineffective treatment was also common in community-acquired infections, where ESBL producers are normally unexpected, although this appears to be a relevant phenomenon in line with cohorts from Europe and the USA [2,4,5]. The likelihood of inactive antimicrobial treatment for bacteraemia due to multi-drug-resistant Gram-negative pathogens has been reported by other studies [6,7] and associated with adverse outcomes.

In this retrospective study, patients with healthcare-associated bacteraemia were older and had higher Charlson Comorbidity Index scores compared with patients with community- and hospital-acquired infections, reflecting the fragility of this population, exposed to the risk of contracting ESBL infections due to recent hospitalization, antimicrobial administration or ongoing medical treatment [8]. ESBL Enterobacterales causing healthcare-associated infections had higher rates of piperacillin-tazobactam resistance and multi-drug resistance compared with the other isolates, possibly contributing to ineffective empirical treatment.

Septic shock and high Pitt score were, not surprisingly, among the factors associated with mortality [2]. Interestingly, an unknown source of bacteraemia was also associated with mortality after adjusting for confounders, reflecting the importance of prompt source control [8].

This study has several limitations, including its retrospective single-centre design and its small sample size. Moreover, since this study was conducted, new anti-ESBL agents have become available which may be used as empirical treatment in some settings. This limits the generalizability of the study data to the current scenario.

Overall, the results highlight how efforts are needed to improve the recognition and management of patients with healthcare-associated bacteraemia due to ESBL-producing Enterobacterales. To this extent, antimicrobial stewardship programmes targeting hospitals, healthcare facilities and the community are essential.

Funding

This study was partially funded by the Italian Ministry of Health RC 2023.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki. The study was submitted to the approval pathway established by the ethics committee of the study hospital for monocentric retrospective studies (Prot. 5329 of 12/03/2015) and approved [Approval No. 1536 (2018)]. Due to the retrospective design, patient consent was not required.

Conflict of interest statement

None declared.

Acknowledgements

The authors wish to thank Liliane Chateneud for support with the statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.01.005.

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