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Clinical outcome of extended-spectrum beta-lactamase-producing *Escherichia coli* bacteremia in an area with high endemicity

Kelvin K.W. To [a,b,c], Wai-U Lo [c], Jasper F.W. Chan [c], Herman Tse [a,b,c], Vincent C.C. Cheng [c], Pak-Leung Ho [a,b,c,*]

[a] *Research Centre of Infection and Immunology, Pokfulam, Hong Kong Special Administrative Region, China*
[b] *State Key Laboratory for Emerging Infectious Diseases, Pokfulam, Hong Kong Special Administrative Region, China*
[c] *Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Pokfulam, Hong Kong Special Administrative Region, China*

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SUMMARY

Objectives: This study assessed the impact of discordant empirical antibiotic therapy on the outcome of bacteremia caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*.
Methods: The clinical features and outcomes of a cohort of patients hospitalized with ESBL *E. coli* bacteremia between 2007 and 2008 were retrospectively reviewed. The effect of different antimicrobial regimens on patient outcomes was analyzed.
Results: ESBL *E. coli* accounted for 24.2% (207/857) of *E. coli* bacteremia cases. The urinary tract (43.6%) was the most common source of infection, followed by the hepatobiliary tract (23.0%). Discordant empirical antibiotic therapy was given to 52.0% patients. Admission to the intensive care unit was associated with the use of a carbapenem as empirical antibiotic therapy ($p < 0.001$). Univariate analysis revealed no significant differences in 30-day mortality rates between patients receiving concordant and discordant empirical antibiotic therapy (23.5% vs. 19.8%, $p = 0.526$), carbapenem and non-carbapenem empirical antibiotic therapy (29.8% vs. 19.1%, $p = 0.118$), beta-lactam/beta-lactam inhibitor combinations (BLBLIs) and non-BLBLIs empirical antibiotic therapy (20.3% vs. 22.3%, $p = 0.734$), cephalosporin and non-cephalosporin empirical antibiotic therapy (19.7% vs. 22.6%, $p = 0.639$), and fluoroquinolone and non-fluoroquinolone empirical antibiotic therapy (8.3% vs. 22.4%, $p = 0.251$). The findings were confirmed by multivariate analysis.
Conclusions: Despite a high proportion of discordant empirical antibiotic therapy, ESBL production had little effect on 30-day mortality. Whether the observation can be applied to different ESBL types is unknown and warrants further study.

1. Introduction

In the last 5 to 10 years, the incidence of infections caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBL) has increased rapidly, mainly attributed to the successful distribution of CTX-M enzymes among *Escherichia coli* causing urinary tract and bacteremic infections.[1–3] A particularly challenging issue is that CTX-M-producers are increasingly recovered from patients with community-onset infections, especially those with minimal or absent healthcare risks.[4] We have previously shown that the CTX-M enzymes are emerging in Hong Kong, China.[5–7] Among female outpatients with urinary tract infections, the prevalence of ESBL was 6.6% in 2004 and 10% in 2005.[6] All ESBL-producers were found to carry CTX-M-type beta-lactamases.[6] For bacteremia, the ESBL rate for both community-onset and hospital-onset episodes increased from 8.9% and 20.3%, respectively, in 2000 to 25.5% and 43.5%, respectively, in 2010.[8] Consequently, there is a need to assess how antimicrobial strategies should be modified to minimize the impact of antimicrobial resistance on patient care.

As the majority of ESBL-producing *E. coli* remain susceptible to the carbapenems, this class of antibiotics is widely accepted as providing the agents of choice in treating patients with serious or bacteremic infections caused by such organisms. However, whether or not other in vitro active agents such as amoxicillin–clavulanate, piperacillin–tazobactam, and fluoroquinolones can be administered for the treatment of bacteremia remains controversial.[9,10] Furthermore, there is debate on whether the third-generation cephalosporins are effective against low-minimum inhibitory concentration (MIC) ESBL-producers.[11] While some studies have demonstrated that inappropriate initial therapy is

* Corresponding author.
E-mail address: plho@hkucc.hku.hk (P.-L. Ho).

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associated with excess mortality in infections caused by ESBL *E. coli*,[12,13] others have not found such an association, especially in low-risk bacteremia and when therapy involves agents with some in vitro activity against the infecting ESBL-producers.[14] Therefore, the present study was conducted to describe the impact of ESBL production and inappropriate empirical therapy on bacteremia caused by ESBL-producing *E. coli*.

2. Methods

2.1. Setting and patient description

This study was performed at Queen Mary Hospital, a 1650-bed university-affiliated teaching hospital. In our hospital, as a general recommendation for empirical treatment, cefuroxime or amoxicillin–clavulanate are given to patients with mild bacterial infections, while piperacillin–tazobactam or carbapenems are reserved for patients with moderate or severe infections.[15] Adult patients aged 18 years and above with bacteremia due to *E. coli* from January 2007 to December 2008 were identified using the laboratory information system. Each patient was recruited only once. For patients with more than one episodes of bacteremia, the first episode was used in the analysis. The clinical information of patients infected with ESBL-producing strains was retrieved from the Clinical Management System. Patients were excluded if clinical records were not accessible for review or antibiotics were not given before death. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

2.2. Bacterial identification and antimicrobial susceptibility testing

The BACTEC 9240 blood culture system (Becton Dickinson, MD, USA) was used for processing of blood specimens. Bacterial isolates were identified using the VITEK GNI system (bioMérieux Vitek Inc., Hazelwood, MO, USA). Antibiotic susceptibility testing was performed using the Kirby–Bauer disk diffusion method and interpreted in accordance with the Clinical and Laboratory Standards Institute criteria.[16]

2.3. Definitions

Healthcare risk factors included hospital onset (first positive blood culture collected $\geq$48 h after admission), prior hospitalization within 1 year before the positive blood culture, and residency in a residential care home for the elderly. Community-associated infection was defined as infection in a patient who did not have any healthcare risk factors, while hospital-associated infection was infection in those who had any healthcare risk factor. The Charlson comorbidity index was used to measure comorbidity using the International Classification of Diseases ninth revision (ICD-9) coding and verified by a review of the records.[17] Empirical antibiotic therapy was defined as antibiotics given before the culture results were reported, whereas known pathogen therapy was defined as antibiotics given after the culture results were reported. Concordant therapy was defined as the use of carbapenems, beta-lactam/beta-lactam inhibitor combinations (BLBLIs), or fluoroquinolones to which the isolated strain was susceptible. Discordant therapy was defined by in vitro resistance to the antibiotics given. The use of third-generation cephalosporins was considered to be discordant irrespective of in vitro results.[11]

2.4. Statistical analysis

The statistical analysis was performed using SPSS software, version 17.0 for Windows. The Chi-square test was used for comparison of categorical variables. Univariate and multivariate analyses were used to assess factors that affect patient outcome. The following parameters were included in the multivariate analysis: age, sex, comorbidities, source of infection, and empirical antibiotic therapy. For the calculation of length of stay, patients for whom the length of stay could not be determined were excluded. A p-value of < 0.05 was considered to be statistically significant.

3. Results

During the 24-month study period, a total of 857 adult patients had a positive blood culture for *E. coli*. Of these, 207 (24.2%) had ESBL *E. coli* bacteremia. Two patients were excluded because the clinical records were not available for review and one patient was excluded because antimicrobials were not given before death. Therefore, 204 patients were included in this study (Table 1). Overall, 8.3% (17/204) were classified as having community-associated infections and 91.7% (187/204) as having hospital-associated infections. Among those with hospital-associated infections, 32.1% (60/187) were classified as having a hospital-onset infection, 38.5% (72/187) were residents of a residential care home for the elderly, and 89.8% (168/187) had a history of prior hospitalization within 1 year. More than two-thirds of the patients were aged 65 years or above. At the time of blood culture collection, more than 50% of patients were located in the medical ward. The urinary tract (43.6%) was the most common source of infection, followed by the hepatobiliary tract (23.0%).

Table 2 shows the results of susceptibility testing. All strains were susceptible to imipenem. Over 90% of the strains were susceptible to piperacillin–tazobactam or amikacin.

The use of antibiotics is illustrated in Figure 1. There was no significant difference in the Charlson comorbidity score between patients with different empirical antibiotic therapy regimens. Patients who required admission to the intensive care unit were more likely to receive a carbapenem than those who did not (70% (14/20) vs. 17.9% (33/184), $p < 0.001$). Concordant empirical antibiotic therapy was given to 98 (48.0%) patients, including 22 patients who were concurrently treated with more than one in vitro active antibiotic. Discordant empirical antibiotic therapy was given to 106 (52.0%) patients. The mean duration of discordant

Table 1
Baseline characteristics of the 204 patients with bacteremia due to ESBL-producing *Escherichia coli*

Characteristics	*n* (%)
Demographics	
Female sex	100 (49.0)
Age $\geq$65 years	139 (68.1)
Mean Charlson comorbidity index (IQR)	2 (1–4)
Specialty where first positive culture was taken	
Medicine	112 (54.9)
Surgery	60 (29.4)
Intensive care unit	8 (3.9)
Accident and emergency	11 (5.4)
Other	13 (6.4)
Source of infection	
Urinary tract	89 (43.6)[c]
Biliary tract/liver	47 (23.0)
Intra-abdominal[a]	14 (6.9)
Pneumonia	11 (5.4)
Other[b]	11 (5.4)
Unknown	32 (15.7)

ESBL, extended-spectrum beta-lactamase; IQR, interquartile range.
[a] Includes peritonitis, pancreatitis, perianal abscess, and diverticulitis.
[b] Includes neutropenic fever (n = 8), wound infection (n = 2), and catheter-related infection (n = 1).
[c] Sixty-four patients did not have a urinary catheter, 21 patients had a urethral catheter, and four patients had a nephrostomy tube.