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Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing *Escherichia coli* bacteraemia: a five-year study☆

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SUMMARY

Background: The impact of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) bacteraemia on outcome remains controversial.
Methods: A retrospective analysis of the prevalence, risk factors, clinical features, and outcomes of all ESBL-EC bacteraemia in one French hospital over a 5-year period was performed. A case–control study was undertaken: cases had at least one ESBL-EC bacteraemia and controls a positive non-ESBL-EC bacteraemia.
Results: The prevalence of ESBL-EC bacteraemia increased from 5.2% of all positive *E. coli* blood cultures in 2005 to 13.5% in 2009 ($p < 0.003$). CTX-M represented 70% of ESBL-EC bacteraemia strains, and strains were not clonally related. On adjusted analysis, the only significant risk factor for ESBL-EC bacteraemia was a previous ESBL-EC colonization (odds ratio 11.3, 95% confidence interval 1.2–107; $p = 0.003$). Initial antimicrobial therapy was less frequently adequate in the ESBL-EC group (48% vs. 85%; $p = 0.003$). The presence of ESBL-EC bacteraemia was not associated with a longer hospital stay ($p = 0.088$). Day 30 mortality was high, but not significantly different in the two groups (30% vs. 27%; $p = 0.82$).
Conclusion: The prevalence of ESBL-EC bacteraemia has been increasing dramatically. Previous colonization with ESBL-EC was a strong risk factor for ESBL-EC bacteraemia. More inadequate initial antimicrobial therapy was noted in the ESBL-EC group, but mortality and length of hospital stay were not significantly different from those of patients with non-ESBL-EC bacteraemia.

1. Introduction

Infections due to extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* have become a major health problem. ESBL-producing *Escherichia coli* (ESBL-EC), especially of the CTX-M type, have increased dramatically worldwide.[1–3] Risk factors for ESBL infection have been identified and include age, comorbidities, poor functional status, recurrent urinary tract infections, intensive care unit stay, prolonged hospital stay, previous use of antibiotics, and colonization with ESBL.[1,4] Studies performed after the year 2000 have reported the risk of bacteraemia in patients colonized with ESBL-producing bacteria to range from 8.5% to 25%.[5,6] Treatment options for infections due to ESBL strains are limited, because resistance genes are harboured

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by plasmids that also carry genes for resistance to other antibiotics.[2] The impact of ESBL *E. coli* bacteraemia (ESBL-EC bacteraemia) on mortality is controversial. Some studies have shown that mortality is associated with inappropriate antimicrobial therapy, irrespective of ESBL production, whereas others have reported an increased mortality due to ESBL.[7–12]

The aim of the current study was thus to assess the prevalence and risk factors for ESBL-EC bacteraemia and to analyse their impact on length of hospital stay and on day 30 mortality in hospitalized patients.

2. Methods

Prevalence was studied using data from the Microbiology Laboratory of Saint Louis Hospital, a 550-bed tertiary hospital with major clinical activity in the areas of HIV, haematology, and oncology. Data on all ESBL-EC and non-ESBL-EC bacteraemia from January 2005 to December 2009 were collected. A retrospective case–control study was then conducted, and all hospitalized adults from January 2005 to December 2008 with at least one episode of bacteraemia due to ESBL-EC were included for analysis. This study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki. In this observational research, no additional medical procedure was performed and all data were retrieved from the medical charts of the treated patients. All information was, however, given to the patients and, in accordance with French legislation, patients could refuse the use of their medical data. Baseline characteristics at the date of the first positive blood culture drawn, clinical and microbiological data, antibiotic therapy, and outcomes were recorded carefully for each patient.

Cases were defined as adults with blood culture(s) yielding ESBL-EC during the study period. In the case of several positive ESBL-EC bacteraemia during the same infectious episode, only the first positive blood culture was considered for analysis. For each case, one control was selected among hospitalized patients with a positive non-ESBL-EC blood culture and matched to the closest date of an ESBL-EC bacteraemia positive defining-case.

The following data were retrieved from the medical charts: age, gender, underlying diseases and comorbidities (HIV, haematological malignancies, solid tumour, diabetes mellitus, solid organ transplant), severity as assessed by the APACHE II score (the Acute Physiology and Chronic Health Evaluation is a general prognostic model for mortality calculated at admission), severe neutropenia (absolute neutrophil count (ANC) $<100/mm^3$), current chemotherapy, antibiotic use during the past 3 months, ESBL-EC colonization during the past 6 months, antibiotic susceptibility of the isolated strain, initial antibiotic therapy, length of hospital stay, and day 30 mortality (defined as the time from the first positive blood culture until discharge or death). Bacteraemia was classified as nosocomial, healthcare-related, or community-acquired, as described previously.[13] The source of bacteraemia was considered to be urinary, catheter, digestive, or respiratory when the strains recovered from the blood culture and from the source were phenotypically similar. Rare locations were classified as 'other', and when the portal of entry could not be identified clearly, the source of bacteraemia was classified as 'unidentified'.

An adequate first antibiotic regimen was defined as a regimen containing at least one in vitro active drug, at the recommended dose, and initiated within 24 h after the blood sample was drawn. If one or more of these conditions was not fulfilled, then antimicrobial therapy was considered inadequate. Isolates were identified using the API System (bioMérieux, Marcy l'Etoile, France). Strain susceptibility to antibiotics was determined by disk diffusion method and interpreted according to the French Society for Microbiology criteria with the 2008 susceptibility breakpoints (ESBL-EC strains were interpreted as resistant to amoxicillin–clavulanate, piperacillin–tazobactam, and to broad-spectrum cephalosporins).[14] ESBL production was detected by double-disk synergy test between clavulanate and third-generation cephalosporins. ESBL type was identified by ESBL KPC Microarray (Check Points, Wageningen, Netherlands), according to the manufacturer's instructions. Previous colonization strains were also studied using the same procedure. ESBL-EC colonization strains were obtained by rectal swab during the 6 months prior to the onset of bacteraemia for all patients in the non-ESBL-EC group and for 31 (76%) of the patients in the ESBL-EC group. ESBL-EC infection was defined as the first positive ESBL-EC blood culture during the study period. Genotype comparison between ESBL-EC bacteraemia strains and colonization strains from the same patients was performed using DiversiLab system software, version 3.3.40 (bioMérieux).[15] Relationships between DiversiLab patterns were designated as recommended in the manufacture's guidelines: different strains (similarity $<92\%$) with three or more band differences, or similar strains (similarity $\geq 92\%$) with two or fewer band differences.

2.1. Statistical analysis

The trend in ESBL-EC bacteraemia prevalence over time was compared with a Chi-square test for trend.

Baseline characteristics of the patients in the ESBL-EC and non-ESBL-EC groups were compared by Wilcoxon signed-rank tests and Liddell tests, accounting for the pair-matched design of the study. The cause-specific proportional hazards model with death as a competing risk was used for length of stay.

Conditional logistic regression was used for adjusted analysis. The variables introduced into the multivariate analysis included those with a marginal p-value of <0.15. APACHE II score was included in the model as a continuous variable.

Since day 30 mortality of matched patients had no reason to be correlated (matching only on the date of blood culture, with no major changes in outcome over the study period), the outcome analysis did not account for matching. It was nevertheless checked that intra-pair correlation was negligible for outcome (intra-class correlation coefficients <0.0001). Risk factors for day 30 mortality were analysed by logistic regression. Since there were only 23 deaths, only three variables were included in the model in order to limit over-fitting. Before including the variable 'inadequate antimicrobial therapy' into the model, an interaction with ESBL-EC groups was tested. As a significant interaction was observed, results of the adjusted analysis on mortality are detailed with the effect of inadequate antimicrobial therapy in the ESBL-EC and non-ESBL-EC groups.

A sensitivity analysis was undertaken for patients in the ESBL-EC group treated with piperacillin–tazobactam, according to the current Comité de l'antibiogramme de la Société Française de Microbiologie (CA-SFM) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2015 guidelines (http://www.sfm-microbiologie.org/.../casfm/CASFM_EUCAST_V1_2015.pdf): ESBL strains were tested using the Etest method and considered susceptible when the minimum inhibitory concentration (MIC) for piperacillin–tazobactam was ≤ 8 mg/l. Patients were classified as having received an adequate treatment if the strain was susceptible and treatment initiated within 24 h after the first blood culture was drawn.

Analyses were performed using R statistical software, version 2.10.1 (R Development Core Team, Vienna, Austria). All statistical analyses were two-sided and p-values less than 0.05 were considered significant.