International Journal of Infectious Diseases 39 (2015) 62–67

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) infections: are carbapenem alternatives achievable in daily practice?

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ARTICLE INFO

Article history:
Received 10 May 2015
Received in revised form 27 July 2015
Accepted 22 August 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Extended-spectrum beta-lactamase
De-escalation
Carbapenem

SUMMARY

Objectives: To avoid the use of carbapenems, alternatives such as cephamycin, piperacillin–tazobactam, and others are suggested for the treatment of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) infections. The aim of this study was to evaluate the frequency and the feasibility of antimicrobial de-escalation for ESBL-PE-related infections.

Methods: A prospective observational, bi centric cohort study was conducted. All patients with ESBL-PE infections were included. De-escalation was systematically suggested if patients were clinically stable and the isolate was susceptible to possible alternatives.

Results: Seventy-nine patients were included: 36 (45.6%) were children, 27 (34.1%) were hospitalized in intensive care units, and 37 (47%) were immunocompromised. Urinary tract infections, pneumonia, and catheter-related bloodstream infections accounted for 45.6%, 19%, and 10%, respectively, of the cohort. *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* were the three most frequent causative organisms isolated. On day 5, 47 (59.2%) of the patients were still receiving carbapenems. Antimicrobial resistance (44.7%), infection relapse (26.9%), and clinical instability (19.2%) were the most important reasons for not prescribing alternatives. *E. coli*-related infections appeared to be a protective factor against maintaining the carbapenem prescription (odds ratio 0.11, 95% confidence interval 0.041–0.324; $p = 0.0013$).

Conclusions: In clinical practice, less than 50% of patients with ESBL-PE-related infections were de-escalated after empirical treatment with carbapenems.

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1. Introduction

Since the 1980s, extended-spectrum beta-lactamase (ESBL)-producing isolates have spread worldwide.[1,2] These isolates are often multidrug-resistant, and carbapenems are often regarded as a major antibacterial drug.[3,4] Massive prescription of these drugs has ecological consequences.[5] Indeed it increases the rise and spread of carbapenemase-producing *Enterobacteriaceae*[6] and the rate of subsequent multidrug-resistant bacteria-related infections.[3,4]

Several studies have tried to assess the safety and efficacy (mortality and length of hospital stay) of the use of non-carbapenem drugs for the treatment of ESBL-related infections.[7–10] Major studies have been non-randomized and have shown conflicting results.[8] In patients with susceptible ESBL-producing *Escherichia coli* bloodstream infections (BSI), Rodríguez-Baño et al.[7] showed

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http://dx.doi.org/10.1016/j.ijid.2015.08.011
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that there was no difference in outcome between patients treated with carbapenems or beta-lactam/beta-lactam inhibitor (BLBLI) combinations (including piperacillin–tazobactam (PTZ) and amoxicillin–clavulanate (AAC)). However that cohort study was composed mainly of patients with bacteraemia originating from the urinary tract and did not take into account minimum inhibitory concentrations (MICs). Despite theoretical microbial susceptibility (as defined by the Clinical and Laboratory Standards Institute criteria), recent studies have reported suboptimal clinical and microbiological outcomes in patients treated with alternatives to carbapenems for infections with ESBL-producing strains.[11] In this setting, the use of cephalosporins (as compared to carbapenems) has also been associated with increased mortality, even when the MIC for *Enterobacteriaceae* remains within the susceptible range.[12,13] Conversely, the use of fluoroquinolones is also frequently restricted by antimicrobial co-resistance of ESBL strains.[4] Therefore, non-carbapenem alternatives may be used with caution in selected cases of infection with ESBL-producing strains, but clear guidelines are currently lacking.[14–16]

The primary aims of this observational prospective cohort study were to identify the rate of non-carbapenem alternative prescription and to evaluate the frequency and factors associated with the omission of de-escalation. The secondary aim was to identify daily practice factors associated with carbapenem prescription (either as empirical or as definitive therapy) in the setting of ESBL infections.

2. Materials and methods

2.1. Study design

This observational prospective study was performed in two French university hospitals (Hôpital Necker Enfants Malades, Paris, and Hôpital Henri Mondor, Créteil) from May 2012 to January 2013. Antimicrobial stewardship teams are well established in these hospitals, each composed of a pharmacist and a full-time infectious disease physician, assisted by one or two fellows.

At the time the antimicrobial stewardship team was alerted by the microbiologist, a first consultation (at day 0 or day +1) consisted of encouraging prescribers to adapt their treatment in accordance with local recommendations. A second visit was systematically performed when antimicrobial susceptibility tests were obtained. An advice and an evaluation were systematically delivered to improve and adapt antibiotic prescription. De-escalation was systematically proposed when clinical and microbiological data allowed it. Practitioners were free to follow or not these recommendations.

All consecutive patients (adults and children) treated for ESBL-producing *Enterobacteriaceae* (ESBL-PE) infections were included prospectively. Using a computer-generated alert system, the antimicrobial stewardship team conducted a systematic post-prescription review of all carbapenem prescriptions. All ESBL-PE documented infections were recorded daily by a microbiologist who notified the antimicrobial team. During the study period, a review of all antibiotic prescriptions initiated for ESBL-PE documented infections was also systematically performed. The team reviewed all prescriptions successively within the first 48 h, when antimicrobial susceptibility tests were available, and finally on day 5. Data collected at inclusion consisted of demographic characteristics (age, sex), comorbid conditions, Charlson's weighted index of morbidity, immunodeficiency, previously known ESBL rectal carriage for the last 6 months, and the clinical severity according to the Bone criteria.[17] Immunodeficiency was defined as neoplasia with recent chemotherapy (less than 30 days before infection), neutropenia (neutrophil count $<0.5 \times 10^9$ cells/l), treatment with glucocorticosteroids and/or other immunosuppressants within the last month, solid organ or bone marrow transplantation recipient, or AIDS (CD4 cell count <200/ml, or other evidence of AIDS as defined by the US Centers for Disease Control and Prevention (CDC)).[18]

The primary source of infection was determined according to the CDC criteria,[19] or otherwise defined as primary bacteraemia with no determined portal of entry.

Bacterial identification was performed in both hospitals with the commercially available Vitek 2 system or with the API 20 E, API 20NE strips (bioMérieux, Marcy l'Etoile, France). Microbiological ESBL diagnosis was carried out according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.[20] In vitro antimicrobial susceptibility testing was performed with the disk diffusion method or with the Vitek 2 system in accordance with the guidelines of the Antibiogram Committee of the French Microbiological Society.[21] Clinical outcome was recorded at hospital discharge.

Two non-mutually exclusive cohorts of patients (receiving either carbapenems or an alternative) were constructed and analyzed separately. The empirical therapy cohort (ETC) included patients during the first 24 h following positive microbiological results (day 0) and the definitive therapy cohort (DTC) included patients treated according to MIC results from day 5 until the end of antimicrobial therapy.

2.2. Alternatives to carbapenems

Third-generation cephalosporins (3GC), PTZ, and cephamycins were used as carbapenem alternatives, as per EUCAST recommendations. Thus, strains with a MIC <8 mg/l were considered susceptible to PTZ and strains with a MIC <1 mg/l were considered susceptible to 3GC.

2.3. Statistical analysis

2.3.1. Descriptive analysis

A descriptive analysis was performed using the median and interquartile range (IQR) or the mean and standard deviation (SD) for the quantitative variables, and the number and proportion for the qualitative variables.

2.3.2. Factors associated with the maintenance of carbapenems

Factors associated with the maintenance of carbapenem therapy were identified using both univariate and multivariate analysis, using a conditional logistic regression model. Analyses were stratified on the centre and hospitalization in a ward dedicated to paediatric care. Associations are reported as the odds ratio (OR) and 95% confidence interval (CI). Factors considered for the multivariate model were those with at least 10 events, without missing data, that were non-collinear with other factors (with a significance level $<10^5$), and associated with the status (maintenance or withdrawal of carbapenem therapy) on univariate analysis with a significance level (p-value) less than 0.20. Factors included in the final multivariate model were selected using a forward stepwise selection procedure based on the Akaike Information Criterion (AIC). The statistical analysis was performed by T.D. using R program version 3.02 (R Foundation for Statistical Computing, Vienna, Austria). This observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22]

3. Results

During the study period, 79 ESBL-PE-related infections were included. Baseline characteristics of the patients are detailed in

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