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Empirical third-generation cephalosporin therapy for adults with community-onset Enterobacteriaceae bacteraemia: Impact of revised CLSI breakpoints

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ABSTRACT

Third-generation cephalosporins (3GCs) [ceftriaxone (CRO) and cefotaxime (CTX)] have remarkable potency against Enterobacteriaceae and are commonly prescribed for the treatment of community-onset bacteraemia. However, clinical evidence supporting the updated interpretive criteria of the Clinical and Laboratory Standards Institute (CLSI) is limited. Adults with community-onset monomicrobial Enterobacteriaceae bacteraemia treated empirically with CRO or CTX were recruited. Clinical information was collected from medical records and CTX MICs were determined using the broth microdilution method. Eligible patients (n = 409) were categorised into de-escalation (260; 63.6%), no switch (115; 28.1%) and escalation (34; 8.3%) groups according to the type of definitive antibiotics. Multivariate regression revealed five independent predictors of 28-day mortality: fatal co-morbidities based on McCabe classification [odds ratio (OR) = 19.96; P < 0.001]; high Pitt bacteraemia score (≥4) at bacteraemia onset (OR = 13.91; P < 0.001); bacteraemia because of pneumonia (OR = 5.45; P = 0.007); de-escalation after empirical therapy (OR = 0.28; P = 0.03); and isolates with a CTX MIC ≤ 1 mg/L (OR = 0.17; P = 0.02). Of note, isolates with a CTX MIC ≤ 8 mg/L (indicated as susceptible by previous CLSI breakpoints) were not associated with mortality. Furthermore, clinical failure and 28-day mortality rates had a tendency to increase with increasing CTX MIC (γ = 1.00; P = 0.01). Conclusively, focusing on patients with community-onset Enterobacteriaceae bacteraemia receiving empirical 3GC therapy, the present study provides clinically critical evidence to validate the proposed reduction in the susceptibility breakpoint of CTX to MIC ≤ 1 mg/L.

1. Introduction

Bacteraemia is a life-threatening condition associated with high morbidity and mortality [1] and is typically complicated by severe sepsis or septic shock [2]. Third-generation cephalosporins (3GCs), such as cefotaxime (CTX) and ceftriaxone (CRO), have remarkable potency against all Enterobacteriaceae and have been established as an appropriate parenteral treatment of various community-onset infections caused by susceptible organisms, such as complicated urinary tract infections, lower respiratory tract infections, bacterial meningitis, bacteraemia, connective tissue infections, pelvic inflammatory disease, intra-abdominal infections and Lyme disease [3,4].

The Clinical and Laboratory Standards Institute (CLSI) has suggested that detecting extended-spectrum β-lactamase (ESBL)-producers is unnecessary and has adjusted all cephalosporin sensitivity breakpoints in the current interpretive criteria of CTX and CRO for Enterobacteriaceae bacteraemia established since January 2010 [5,6]. Based on updated interpretive breakpoints, isolates with a CTX (or CRO) minimum inhibitory concentration (MIC) of ≤1 mg/L are referred to be susceptible, 2 mg/L as intermediate and ≥4 mg/L as resistant to CTX (or CRO) [5]. Despite this revision being based on re-evaluation of in vitro susceptibility data,

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pharmacokinetic/pharmacodynamic analyses and animal experiments, updated clinical evidence for this revision is lacking and the clinical impact of such a revision remains unknown. In addition, based on previous studies [7,8], Enterobacteriaceae account for the vast majority of causative pathogens of community-onset bacteraemia. The aim of this study was therefore to evaluate the clinical outcome of adults with community-onset Enterobacteriaceae bacteraemia with different CTX MICs when they were empirical treated with 3GCs (CRO or CTX).

2. Materials and methods

2.1. Study design and population

A retrospective observational study was conducted at a medical centre in southern Taiwan. The hospital institutional review board approved the study, which was reported according to the format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [9].

Bacterial growth in blood cultures of adults with blood cultures sampled in the emergency department (ED) between January 2008 and December 2013 was screened in a computer database. Among patients with Enterobacteriaceae bacteraemia, clinical information was retrieved from medical records using a predetermined case record form, including demographic data, initial syndrome, vital signs, laboratory data, co-morbidities, duration and type of antimicrobial agents, bacteraemia source, length of hospitalisation and clinical outcome. If there were multiple bacteraemic episodes, only the first episode for each patient was included. Finally, adults with community-onset Enterobacteriaceae bacteraemia who were treated empirically with intravenous CTX or CRO were enrolled into the study. Patients with delayed appropriate antibiotic therapy were excluded based on previous criteria of the CLSI in 2009 [6] because an adverse impact of delayed appropriate antibiotic therapy on the outcome of bacteraemic patients in the ED has been observed [10]. In addition, patients not receiving a standard dosage of antibiotics based on the Sanford Guide [11], those with combination therapy and those with incomplete clinical information were excluded. Based on the type of definitive antibiotics, all eligible patients were categorised into those definitively switched to narrow-spectrum antibiotics (de-escalation group), those treated with the same drug as empirical therapy (no switch group) and those definitively switched to broad-spectrum antibiotics (escalation group).

The primary endpoint was crude 28-day mortality. To avoid underestimating the mortality rate for a patient who was discharged earlier than 28 days after bacteraemia onset and who did not return to the outpatient clinic, outcome information was retrieved by telephone contact. Patients unable to be reached by telephone were excluded.

2.2. Microbiological methods

Blood cultures were incubated in a BD BACTEC^{TM} 9240 blood culture system (BD Diagnostic Systems, Sparks, MD) for 5 days at 35 °C and Enterobacteriaceae were identified using the GNI Card of the VITEK system (bioMérieux, Lyon, France). CTX MICs were determined by the broth microdilution method in a fully automated commercial susceptibility testing system (VITEK® 2; bioMérieux, Durham, NC) using antimicrobial susceptibility testing card AST-GN07. For *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis*, the presence of ESBLs was determined by a phenotypic confirmatory test with cephalosporin/clavulanic acid combination disks as recommended by CLSI guidelines [6].

2.3. Definitions

Community-onset bacteraemia indicates that the place of onset of the bacteraemic episode is the community, which includes long-term healthcare facility- and community-acquired bacteraemia, as previously described [12]. Monomicrobial bacteraemia was defined as the isolation of one microbial species from a single bacteraemic episode. As previously described, drugs prescribed for <24 h were not taken into consideration [10]. Because susceptibility data were available approximately 3 days after bacteraemia onset, empirical antibiotic therapy was defined as the drug prescribed within 3 days after bacteraemia onset, whereas definitive therapy referred to the antibiotic prescribed when the susceptibility results were available. The Pitt bacteraemia score, a previously validated scoring system based on vital signs, use of inotropic agents, mental status, receipt of mechanical ventilation and recent cardiac arrest, was utilised to grade the severity of bacteraemia [13]. Severe sepsis was defined as the coexistence of sepsis and at least one of the following signs or symptoms of acute organ dysfunction or hypoperfusion: metabolic acidosis; arterial hypoxaemia (PaO_2 < 75 mmHg or PaO_2/FiO_2 < 250); oliguria (<0.03 L/h for 3 h or 0.7 L/24 h); coagulopathy (increase in prothrombin time or a drop in platelet count by 50% or to $<100 \times 10^7$/L); or encephalopathy (Glasgow coma score < 14) [14]. Septic shock was defined as the presence of systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mmHg after a crystalloid fluid challenge of 20–30 mL/kg of body weight over a 30-min period or a blood lactate concentration of ≥4 mmol/L [15].

Malignancy included haematological malignancies and solid tumours. Co-morbidities were defined as described previously [16]. The source of bacteraemia was determined clinically based on the presence of an active infection site coincident with bacteraemia or the isolation of a micro-organism from another clinical specimen prior to or on the same date as bacteraemia onset. If the source of bacteraemia could not be assigned to a specific site, it was classified as primary bacteraemia. Crude mortality was used to define death from all causes, whereas the death of a patient with a clinical course suggestive of persistently active infection without an obvious explanation was referred to as sepsis-related mortality. Defervescence, as previously described [17], was defined as an afebrile state in which the body temperature was maintained at <37.0 °C for ≥24 h, and time to defervescence was defined as the period between defervescence and bacteraemia onset (ED arrival). To assess the clinical response to empirical 3GC therapy, a Pitt bacteraemia score at Day 3 after bacteraemia onset was evaluated; patients who became stabilised at Day 3 were indicated by a Pitt bacteraemia score of 0; and those who remained critically ill were indicated by a Pitt bacteraemia score of ≥4. Escalation to broad-spectrum antibiotics after empirical 3GC therapy, no defervescence within 14 days after bacteraemia onset, or a fatal outcome due to sepsis within 28 day after bacteraemia onset was regarded as clinical failure of empirical 3GC therapy.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows v.20.0. (IBM Corp., Armonk, NY). Continuous variables were expressed as the mean ± standard deviation (S.D.) and were compared by Student's *t*-test. Categorical variables were expressed as number and percentage and were compared by χ^2 or Fisher's exact test. All variables with a *P*-value of <0.05 in the univariate analysis were considered for the stepwise backward logistic regression model. Correlation between two continuous variables was analysed by the Spearman's correlation. A *P*-value of <0.05 was considered significant.