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Comparing the therapeutic efficacies of third-generation cephalosporins and broader-spectrum β-lactams as appropriate empirical therapy in adults with community-onset monomicrobial Enterobacteriaceae bacteraemia: a propensity score matched analysis

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ABSTRACT

In this study, the therapeutic efficacy of third-generation cephalosporins (3GCs) was compared with that of broader-spectrum β-lactams (BSBLs) [fourth-generation cephalosporins (4GCs) and carbapenems] as empirical therapy in adults with community-onset monomicrobial Enterobacteriaceae bacteraemia. Compared with those in the 3GC group ($n = 477$), a significantly higher proportion of patients in the BSBL group ($n = 141$) had initial presentation with severe sepsis or septic shock, critical illness (Pitt bacteraemia score ≥4) at bacteraemia onset and fatal co-morbidities (McCabe classification). For propensity score matching, 318 of the 477 patients in the 3GC group were matched with 106 patients in the BSBL group with the closest propensity scores on the basis of five independent predictors of 28-day mortality. After appropriate matching, no significant differences were observed in major baseline characteristics between the 3GC and BSBL groups in terms of causative micro-organism, bacteraemia severity, major source of bacteraemia, major co-morbidities and severity of co-morbidity. Consequently, the early clinical failure rate (12.9% vs. 12.3%; $P = 0.87$), bacteraemia severity (Pitt bacteraemia score ≥4; 4.6% vs. 8.2%; $P = 0.17$) at Day 3, and 3-day (3.8% vs. 7.5%; $P = 0.11$) and 28-day (13.2% vs. 17.0%; $P = 0.33$) crude mortality rates between the two groups were similar. These data suggest that the efficacy of 3GCs is similar to that of 4GCs or carbapenems when used as empirical antimicrobial therapy for community-onset Enterobacteriaceae bacteraemia.

1. Introduction

Bacteraemia is associated with high morbidity and mortality and is usually complicated by severe sepsis or septic shock [1]. Species within the Enterobacteriaceae family are the most common bacterial pathogens causing community-onset bacteraemia [2,3]. Third-generation cephalosporins (3GCs) such as cefotaxime, ceftriaxone and ceftazidime have remarkable potency against the majority of Enterobacteriaceae in the community and have been established as appropriate parenteral treatment for community-onset bacteraemia and various infections caused by susceptible organisms [4–6].

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Fourth-generation cephalosporins (4GCs) and carbapenems exhibit bactericidal activity against highly resistant Enterobacteriaceae, including isolates producing extended-spectrum β-lactamases (ESBLs) [7] and AmpC β-lactamases [8]. In contrast to 3GCs, the 4GCs and carbapenems have been mainly prescribed for definitive therapy for community-acquired infection caused by susceptible micro-organisms [9,10] or for empirical treatment of various hospital-acquired infections, such as pneumonia [11] and febrile neutropenia [12]. In addition, for critically ill patients with community-onset bacteraemia and infections, 4GCs and carbapenems have also been applied for empirical therapy because of their broader spectrum and low minimum inhibitory concentrations (MICs), followed by a de-escalation strategy if the patient becomes stabilised [13,14]. Furthermore, although 3GCs, 4GCs and carbapenems generally have potency against Enterobacteriaceae in Taiwan and the Asia-Pacific community [4–6], no clinical study has compared the therapeutic efficacies of these antibiotics as initial antimicrobial therapy. Therefore, the purpose of this study was to compare the therapeutic efficacy of intravenous (i.v.) 3GCs with that of broader-spectrum β-lactams (BSBLs), including 4GCs and carbapenems, as appropriate empirical therapy in adults with community-onset Enterobacteriaceae bacteraemia.

2. Materials and methods

2.1. Study design and sites

This retrospective cohort study was conducted from January 2008 to December 2013 at the emergency department (ED) of a medical centre in southern Taiwan. The study hospital is a 1200-bed, university-affiliated medical centre with an annual ED census of ca. 70,000 patients. Adult patients with community-onset monomicrobial Enterobacteriaceae bacteraemia were enrolled. The study was approved by the institutional review board of the hospital, and the requirement of obtaining informed consent was waived. Partial clinical information for this study cohort has been published previously [15,16].

2.2. Patient population

During the study period, cultures of patients who underwent blood culture sampling at the ED were screened for bacterial growth using a computer database. For adults with community-onset monomicrobial Enterobacteriaceae bacteraemia, medical information was retrieved from medical records using a predetermined form. Only adults who received i.v. 3GCs, 4GCs or carbapenems as initial antimicrobial therapy were enrolled in this study. In cases with multiple bacteraemic episodes, only the first episode was included for each patient. Patients were excluded if they were administered inadequate empirical therapy, received combination therapy or had incomplete clinical information when the medical records were reviewed.

2.3. Data collection

Demographic and clinical characteristics were collected by retrospectively reviewing the medical records of all eligible patients. Data on age, initial syndrome, vital signs at the ED, co-morbidities, laboratory data, duration and type of antimicrobial agents administered, bacteraemia source, hospital stay, bacteraemia severity (Pitt bacteraemia score), co-morbidity severity (McCabe classification) and patient outcome were collected by two of the authors of the present study, and any discrepancies were resolved by discussion between the authors. Patients who received empirical 3GC monotherapy were categorised as the 3GC group, and those empirically treated with 4GC or carbapenem monotherapy were categorised as the BSBL group. The primary endpoint was crude mortality within 28 days after bacteraemia onset. The time to defervescence, length of hospital stay and mortality were included as variables to determine clinical outcomes. Defervescence and the clinical response to empirical antimicrobial therapy were assessed at 72 h after initial administration of empirical therapy and at the 4- to 28-day follow-up visit after bacteraemia onset.

2.4. Clinical response and outcome

As previously described [17], early clinical responses to empirical therapy, including early clinical failure and defervescence, were assessed at 72 h after bacteraemia onset. Early clinical failure was defined as escalation to broad-spectrum antibiotics or a fatal outcome within 72 h after bacteraemia onset. In addition, late clinical responses, including late clinical failure and time to defervescence, were assessed at the 4- to 28-day follow-up visit after bacteraemia onset. As previously defined [17], late clinical failure of empirical therapy was defined as escalation to broad-spectrum antibiotics after empirical therapy, no defervescence within 14 days after bacteraemia onset or a fatal outcome due to sepsis within 28 days after bacteraemia onset.

2.5. Definitions

Community-onset bacteraemia indicates that the place of onset of the bacteraemic episode is the community, which includes long-term healthcare facility-acquired and community-acquired bacteraemia, as previously described [14,15]. Because susceptibility data were available at ca. 3 days after bacteraemia onset, empirical antibiotic therapy was defined as the drug prescribed within 3 days after bacteraemia onset, whereas definitive therapy was referred to the antibiotic prescribed when the susceptibility result was available [15]. As previously described [17], defervescence was defined as an afebrile state in which the (tympanic) body temperature is maintained at <37.0 °C for ≥24 h, and the time to defervescence was defined as the period between defervescence and bacteraemia onset (ED arrival). Similar to the previous description [17], antimicrobial therapy was considered adequate when the following criteria were fulfilled: (i) an antimicrobial agent was administered as recommended in the Sanford guide [18], including the route and dosage; and (ii) all organisms isolated from blood were susceptible in vitro based on the updated breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) [19]. As previously described [17], inappropriate empirical antibiotic therapy was defined as the first dose of appropriate antimicrobials not being administered within the first 24 h after blood cultures were drawn. Bacteraemia severity was graded according to the Pitt bacteraemia score using a previously validated scoring system based on vital signs, usage of inotropic agents, mental status, receipt of mechanical ventilation and cardiac arrest [14]. Patients with a high Pitt bacteraemia score (≥4) were considered as critical illness, whereas those with a low Pitt bacteraemia score (=0) were considered as stable. Co-morbidities were defined as described previously [20], and malignancies included haematological malignancies and solid tumours.

The prognosis of pre-existing diseases was assessed using a previous delineated classification system (McCabe classification) [21]. Bacteraemia sources were determined clinically on the basis of the presence of an active infection site coincident with bacteraemia or the isolation of a micro-organism from other clinical specimens before or on the same date as that of bacteraemia onset. If the bacteraemia source could not be assigned to a specific site, it was classified as primary bacteraemia.