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Clinical benefits of antimicrobial de-escalation in adults with community-onset monomicrobial *Escherichia coli*, *Klebsiella* species and *Proteus mirabilis* bacteremia

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ABSTRACT

The clinical benefits of an antimicrobial de-escalation strategy were compared with those of a no-switch strategy in bacteremic patients. Adults with community-onset monomicrobial *Escherichia coli*, *Klebsiella* species and *Proteus mirabilis* bacteremia treated empirically using broad-spectrum beta-lactams, including third-generation cephalosporins (GCs), fourth-GC or carbapenems, were treated definitively with first- or second-GCs (de-escalation group), the same regimens as empirical antibiotics (no-switch group), or antibiotics with a broader-spectrum than empirical antibiotics (escalation group). The eligible 454 adults were categorized as the de-escalation (231 patients, 50.9%), no-switch (177, 39.0%), and escalation (46, 10.1%) groups. Patients with de-escalation therapy were more often female, had less critical illness and fatal comorbidity, and had a higher survival rate than patients in the other two groups. After propensity score matching in the de-escalation and no-switch groups, critical illness at onset (Pitt bacteremia score ≥ 4; 16.5% vs. 12.7%; $P = 0.34$) or day 3 (2.5% vs. 2.5%; $P = 1.00$), fatal comorbidity (16.5% vs. 21.5%; $P = 0.25$), time to defervescence (4.6 vs. 4.7 days; $P = 0.89$), hospital stays (11.5 vs. 10.3 days; $P = 0.13$) and 4-week crude mortality rate (4.4% vs. 4.4%; $P = 1.00$) were similar. However, lower antibiotic cost (mean: 212.1 vs. 395.6 US$, $P < 0.001$) and fewer complications of bloodstream infections due to resistant pathogens (0% vs. 5.1%, $P = 0.004$) were observed in the de-escalation group. De-escalation to narrower-spectrum cephalosporins is safe and cost-effective for adults with community-onset EKP bacteremia stabilized by empirical broad-spectrum beta-lactams.

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1. Introduction

Bacteremia is often complicated with severe sepsis or septic shock and is associated with significant healthcare costs [1]. *Escherichia coli*, *Klebsiella* species and *Proteus mirabilis* (EKP) are the leading microorganisms of community-onset bacteremia, which can be linked to various infectious sources, such as urosepsis, intra-abdominal infection, biliary tract infections or liver abscess [2,3].

To improve clinical outcome of patients with critical illness, therapeutic strategies have been developed, including early goal-directed therapy [4], timely administration of appropriate antimicrobial therapy [2,5] and the use of corticosteroids [6]. To achieve early effective empirical therapy, rapid initiation of broad-spectrum antibiotic therapy is recommended before species identification and in vitro susceptibility of causative pathogens are available [7]. However, broad-spectrum antibiotic therapy can lead to the emergence of resistant microorganisms [7,8]. One goal in minimizing the development of antimicrobial resistance is to optimize the choice and duration of empirical antimicrobial therapy. Thus, antibiotic de-escalation has been recommended to reduce selection pressure and possible toxicity, and limit costs, as soon as microbiological results are available [7].

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Clinical implementation of de-escalation strategies has been associated with improved outcome in prospective studies of patients with severe sepsis and septic shock [9], ventilator-associated pneumonia [10] and severe hospital-acquired pneumonia [11]. Recent studies also show the benefits of de-escalation strategies on short-term mortality in critically ill patients with bloodstream infections [12,13]. However, economic issues and impact on resistance issues due to de-escalation strategies have been rarely reported in the literature. Therefore, the aim of this study was to compare the potential advantages of antibiotic de-escalation with those of a no-switch strategy on clinical outcome in adults with community-onset monomicrobial EKP bacteremia.

2. Methods

2.1. Study design and population

This retrospective cohort study was conducted from January 2008 to December 2013 at the emergency department (ED) of a medical center in Southern Taiwan. The study hospital is a 1200-bed, university-affiliated medical center with an annual ED census of approximately 70,000 patients. The study was approved by the institutional review board of the hospital (A-ER-101-213) and was reported using the format recommended by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE); and the requirement to obtain informed consent was waived [14]. Partial clinical information in this cohort has been published [15,16].

All adults with the growth of blood cultures were screened in a computer database. For adults with community-onset monomicrobial EKP bacteremia, clinical information was retrieved from medical records by a predetermined form. Only the patients receiving broad-spectrum cephalosporins (third-generation cephalosporins [third-GCs] and fourth-GCs) or carbapenems as initial therapy were included. In cases of multiple bacteremic episodes, only the first event was included. Patients were excluded if they were treated with inadequate empirical or definitive therapy, or combination therapy, died within 3 days after bacteremia onset, or their clinical information was incomplete.

2.2. Data collection

The following data were collected for eligible patients: demographic and clinical characteristics, including age, initial syndrome, vital signs at the ED, comorbidities, laboratory data, duration and type of antimicrobial agents administered, bacteremia source, hospital stay, bacteremia severity (Pitt bacteremia score), comorbidity severity (McCabe classification) and patient outcome. Patient medical records were reviewed by two authors, and any discrepancy was solved by discussion between the authors. Based on definitive antibiotics, eligible patients were categorized as those definitively treated using first- or second-GCs (de-escalation group), the same agents as empirical antibiotics (no-switch group) and beta-lactams with a broader-spectrum than the empirical agents (escalation group).

The primary endpoint was crude 4-week mortality. The secondary endpoints were 8-week mortality and bloodstream infections due to ESBL-producers, *Candida* or highly-resistant microorganisms within 8 weeks after bacteremia onset, which was often associated with previous broad-spectrum antimicrobial therapy [17]. The time to defervescence, clinical failure, and crude mortality were included as the clinical outcome variables in response to definitive antimicrobial therapy. Antibiotic cost was referred to as an economic outcome. Bacteremia severity was assessed at 72 hours after onset of bacteremia as the baseline for the initiation of definitive therapy. To avoid underestimating the mortality rate, outcome information for discharged patients who were not followed up at outpatient clinics was retrieved by telephone contact. Patients not reached by telephone were excluded.

2.3. Microbiological methods

Blood cultures were incubated in the BACTEC 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) for 5 days at 35 °C, and EKP were identified by a GNI Card of the Vitek system (bioMérieux, Lyon, France). Bacteremic isolates in the study period were collected prospectively and antimicrobial susceptibility was determined by the disk diffusion method, according to the contemporary breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) in 2016 [18]. Extended-spectrum-β-lactamase (ESBL) production was detected by the phenotypic confirmatory test with the cephalosporin-clavulanate combination disks [19].

2.4. Definitions

Community-onset bacteremia indicates that the place of onset of bacteremia is the community, which includes long-term healthcare facilities-associated and community-acquired bacteremia, as previously described [12,15,16]. Drugs prescribed for less than 24 hours were not taken into consideration [12]. Empirical antibiotic therapy was defined as the drug prescribed before the susceptibility data were available, approximately 3 days after bacteremic onset, whereas definitive therapy referred to the antibiotic prescribed after the susceptibility data were available [12]. Antibiotic therapy was considered to be appropriate if the antimicrobial agent was administered using the route and dosage recommended in the Sanford Guide [20], and bacteremic pathogens were susceptible in vitro to the prescribed agent based on the contemporary CLSI breakpoints [18]. As previously described [15,16], appropriate empirical antibiotic therapy was defined as the first dose of appropriate antimicrobial agent administered within the first 24 hours after blood cultures were drawn.

Malignancy included hematological malignancies and solid tumors. Comorbidities were defined as previously described [21], and the prognosis of preexisting diseases was assessed using a delineated classification system (McCabe classification) [22]. The sources of bacteremia were determined clinically based on the presence of an active infection site coincident with bacteremia, or the isolation of a microorganism from other clinical specimens before or on the date of bacteremia onset. If the source of bacteremia could not be assigned to a specific site, it was classified as primary bacteremia. Crude mortality was used to define the 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 [15,16], was defined as an afebrile state in which body temperature was < 37.0 °C for at least 24 hours, and time to defervescence was defined as the period between defervescence and the initiation of antibiotic therapy. A Pitt bacteremia score, a previously validated scoring system based on vital signs, usage of inotropic agents, mental status, receipt of mechanical ventilation and recent cardiac arrest, was utilized to grade the severity of bacteremia [23]. A high Pitt bacteremia score (≥4) indicated critical illness, whereas a low Pitt bacteremia score (=0) indicated stability.

2.5. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science for Windows (Version 20.0; Chicago, IL, USA). Clinical data, demographic data, severity and patient outcome were compared using the Fisher exact or Pearson chi-square test for categorical variables and an independent *t* or Mann–Whitney test for continuous variables. The variables with a *P* value of <0.05 in the

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