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ORIGINAL ARTICLE

The impact of early adequate antimicrobial therapy on 14-day mortality in patients with monomicrobial *Pseudomonas aeruginosa* and *Acinetobacter baumannii* bacteremia

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Abstract The impact of colistin therapy for early adequate antimicrobial therapy on clinical outcomes has rarely been evaluated in patients with *Pseudomonas aeruginosa* bacteremia (PAB) or *Acinetobacter baumannii* bacteremia (ABB). We investigated the impact of early adequate antimicrobial therapy on 14-day mortality in 149 patients with monomicrobial PAB and ABB at two medical centers where colistin treatment was frequently used. Patients who survived the first 14 days of PAB/ABB received adequate antimicrobial therapy within 3 days of bacteremia more frequently than those who died (53.3 vs. 38.6 %), although this finding is not statistically significant ($p = 0.10$). After excluding patients who received adequate colistin therapy, the difference was statistically significant (94.6 vs. 58.8 %, $p = 0.001$). In a multiple regression model excluding patients who received colistin therapy, adequate antimicrobial therapy within 3 days of bacteremia was a preventive factor for 14-day mortality (adjusted OR = 0.23, 95 % CI = 0.07–0.80, $p = 0.02$). In another multiple regression model including patients who received colistin, compared to inadequate antimicrobial therapy, adequate non-colistin therapy was a preventive factor for 14-day mortality (aOR = 0.22, 95 % CI = 0.07–0.78, $p = 0.019$), but adequate colistin therapy was not (aOR = 8.20, 95 % CI = 1.07–62.90, $p = 0.043$). The favorable impact of early adequate antimicrobial therapy on 14-day mortality in patients with monomicrobial PAB/ABB may be lessened in the clinical practice of using colistin frequently. Further studies may be needed to evaluate the clinical impact of colistin therapy in patients with PAB or ABB.

Keywords Gram-negative bacteria · Bloodstream infections · Antimicrobial treatment

Introduction

The increase in the number of infections caused by multidrug-resistant gram-negative bacilli (GNB) is one of the most important issues in modern healthcare [1]. Among various GNB, non-fermentative GNB such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most problematic because of their frequent development of antimicrobial resistance and the limited armamentarium against them [2, 3]. Early use of adequate antimicrobial therapy has been thought to prevent fatal outcomes in patients infected with GNB, based on the results of previous studies of patients with *P. aeruginosa* bacteremia (PAB) or *A. baumannii* bacteremia (ABB) [4–20]. However, the majority of these studies did not consider the use of colistin or did not include patients who received colistin therapy [4–19]. In clinical practice, physicians may encounter serious infections caused by carbapenem-resistant *P. aeruginosa* or *A. baumannii* for which colistin is the only available antimicrobial agent. Therefore, in light of the increasing use of colistin therapy, there is a need to reevaluate the impact of adequate antimicrobial therapy on the outcomes of patients with PAB or ABB.

We investigated the impact of adequate antimicrobial therapy on 14-day mortality in patients with monomicrobial

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PAB and ABB in two medical centers where carbapenem-resistant *P. aeruginosa* or *A. baumannii* was prevalent and colistin therapy was frequently used.

Patients and methods

This study was performed at Chung-Ang University Hospital (CAUH), a 600-bed tertiary care-affiliated hospital, and Chung-Ang University Yongsan Hospital (CAUYH), a 300-bed secondary care-affiliated teaching hospital. Both CAUH and CAUYH are in Seoul, Republic of Korea. Using the computerized databases of the study hospitals, we identified adult patients (≥18 years of age) whose blood cultures had diagnosed monomicrobial bacteremia caused by *P. aeruginosa* and *A. baumannii* between January 2006 and December 2011. Patients were excluded from the analysis if they had polymicrobial bacteremia or no information on 14-day mortality. We reviewed the medical charts of the remaining study patients and collected data on patient demographics, underlying diseases/conditions, Charlson's comorbidity index, initial severity of illness, Pitt bacteremia score, sites of infection, antimicrobial resistance, antimicrobial therapy, and 14-day mortality.

Systemic inflammatory response syndrome (SIRS) criteria, Charlson's comorbidity index, and Pitt bacteremia score were defined as described previously [21–23]. The site of infection was defined as clinically or microbiologically documented. Adequate antimicrobial therapy was defined as the identified organism being susceptible to at least one of the antimicrobial agents administered within 3 days after the onset of bacteremia. Aminoglycoside monotherapy was considered to be an inadequate antimicrobial therapy for *P. aeruginosa* bacteremia. Colistin became available from late 2007 in the study centers. The daily colistin dose was adjusted to serum creatinine levels as follows: ≤1.2 mg/dl, 5.0 mg/kg; 1.3–1.5 mg/dl, 2.5–3.8 mg/kg; 1.6–2.5 mg/dl, 2.5 mg/kg; ≥2.6 mg/dl, 1.5 mg/kg every 36 h; 1.0 mg/kg for patients receiving hemodialysis [24]. Identification and susceptibility testing of clinical isolates were performed using a Vitek II system (bioMérieux, Hazelwood, MO, USA). Antimicrobial susceptibilities were determined according to CLSI criteria [25].

Statistical analysis was performed using SPSS software (version 12.0; SPSS, Chicago, IL, USA). Binary data were compared using a χ^2 test or Fisher's exact test, and continuous scaled data were compared using Student's *t* test or the Mann–Whitney *U* test. Logistic regression analysis was performed to investigate independent risk factors for 14-day mortality. Variables that had a p value < 0.1 in univariate analysis were included in the logistic regression analysis. A backward-selection process was utilized. A p value < 0.05 was considered significant.

Results

During the study period, 171 adult patients were found to have PAB or ABB. Of these patients, 14 were excluded from the analysis because of polymicrobial bacteremia, and 8 were excluded because of the absence of information on 14-day mortality. In all, 149 patients were included in the study. PAB occurred in 81 of 149 patients (54.4 %) and ABB in 68 (45.6 %). The mean age (SD) was 64.2 years (15.3), and more than half (91, 61.1 %) were male. Carbapenem resistance was observed in 63 patients (42.3 %). Fourteen-day mortality occurred in 44 patients (29.5 %).

Characteristics of the patients who died within 14 days of PAB/ABB and those who survived are shown in Table 1. The following characteristics were more commonly observed in patients who died than in those who survived: chronic lung disease, intensive care unit (ICU) care within 1 month before bacteremia, the receipt of chemotherapy within 1 month before bacteremia, neutropenia with 1 week before bacteremia, septic shock, ICU care within a week after bacteremia, lungs as the site of infection, and antimicrobial resistance to ceftazidime, cefepime, ciprofloxacin, piperacillin–tazobactam, and carbapenem. The respective mean Charlson's comorbidity score and Pitt bacteremia score values were higher in patients with 14-day mortality than in those who survived. The frequency of adequate antimicrobial therapy being administered within 3 days of bacteremia was higher in the survivors than in the non-survivors (53.3 vs. 38.6 %), but this was not statistically significant ($p = 0.10$). When excluding patients who received adequate colistin therapy, the survivors more frequently received adequate therapy within 3 days of bacteremia than the non-survivors (94.6 vs. 58.8 %, $p = 0.001$).

Multiple regression analysis was performed to investigate risk factors for 14-day mortality (Table 2). Adequate antimicrobial therapy, including colistin within 3 days of bacteremia, was not a preventive factor for 14-day mortality in the first multiple regression model. However, it was a preventive factor in the second model, which excluded the colistin group. In the third multiple regression model, in which adequate antimicrobial therapy within 3 days of bacteremia was replaced by type of antimicrobial therapy within 3 days of bacteremia, adequate non-colistin therapy was a preventive factor for 14-day mortality compared with inadequate therapy. However, compared to inadequate therapy, adequate colistin therapy was not a preventive factor for 14-day mortality but instead was a risk factor.

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