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.

Table 1 Characteristics of patients who died within 14 days of monomicrobial *Pseudomonas aeruginosa* or *Acinetobacter baumannii* bacteremia and of those patients who survived

Characteristics	Number of patients (%) who died within 14 days (n = 44)	Number of patients (%) who survived within 14 days (n = 105)	Number of patients (%) who had PAB[a] or ABB[b] (n = 149)	p value
Mean age, years (SD)	66.8 (14.6)	63.2 (15.5)	64.2 (15.3)	0.19
Male sex	26 (59.1)	65 (61.9)	91 (61.1)	0.75
P. aeruginosa bacteremia	21 (45.7)	60 (58.3)	81 (54.4)	0.15
A. baumannii bacteremia	25 (54.3)	43 (41.7)	68 (45.6)	
Underlying diseases/conditions				
Solid tumor	14 (31.8)	29 (27.6)	43 (28.9)	0.61
Diabetes	14 (31.8)	25 (23.8)	39 (26.2)	0.31
Chronic lung disease	11 (25.0)	11 (10.5)	22 (14.8)	0.02
Neurological disease	9 (20.5)	33 (31.4)	42 (28.2)	0.17
Hematological malignancy	6 (13.6)	6 (5.7)	12 (8.1)	0.18
Heart failure	4 (9.1)	2 (1.9)	6 (4.0)	0.06
Alcoholism	4 (9.1)	4 (3.8)	8 (5.4)	0.24
Chronic renal failure or hemodialysis	4 (9.1)	5 (4.8)	9 (6.0)	0.45
Liver cirrhosis	3 (6.8)	2 (1.9)	5 (3.4)	0.15
Trauma	1 (2.3)	14 (13.3)	15 (10.1)	0.07
ICU care within 1 month before bacteremia	30 (68.2)	35 (33.3)	65 (43.6)	<0.001
Surgery <1 week before bacteremia	12 (27.3)	44 (41.9)	56 (37.6)	0.09
Chemotherapy <1 month before bacteremia	9 (20.5)	9 (8.6)	18 (12.1)	0.04
Neutropenia <1 week before bacteremia	7 (15.9)	5 (4.8)	12 (8.1)	0.04
Immunosuppressants <1 month before bacteremia	2 (4.5)	3 (2.9)	5 (3.4)	0.63
Charlson's comorbidity score, mean value (SD)	3.7 (2.4)	2.0 (1.8)	2.5 (2.1)	<0.001
Initial severity of illness				
Septic shock	30 (68.2)	12 (11.5)	42 (28.2)	<0.001
ICU care <1 week after bacteremia	35 (79.5)	25 (23.8)	60 (40.3)	<0.001
Pitt bacteremia score, mean value (SD)	5.3 (3.5)	1.5 (1.9)	2.6 (3.0)	<0.001
Site of infection				
Lungs	20 (45.5)	11 (10.5)	31 (20.8)	<0.001
Primary bacteremia	17 (38.6)	53 (50.5)	70 (47.0)	0.19
Urinary tract	2 (4.5)	18 (17.1)	20 (13.4)	0.04
Vascular catheter	1 (2.3)	9 (8.6)	10 (6.7)	0.28
Skin/soft tissue infection	2 (4.5)	1 (1.0)	3 (2.0)	0.21
Biliary tract	1 (2.3)	11 (10.5)	12 (8.1)	0.11
Central nervous system	1 (2.3)	0	1 (0.7)	0.30
Abdomen	0	2 (1.9)	2 (1.3)	1.00
Antimicrobial resistance to				
Cefotaxime	44 (100)	96 (91.4)	140 (94.0)	0.06
Ceftazidime	32 (72.7)	41 (39.0)	73 (49.0)	<0.001
Cefepime	31 (70.5)	44 (41.9)	75 (50.3)	0.001
Ciprofloxacin	30 (68.2)	47 (44.8)	77 (51.7)	0.009
Piperacillin–tazobactam	25 (56.8)	34 (32.4)	59 (39.6)	0.005
Gentamicin	23 (52.3)	39 (37.1)	62 (41.6)	0.09
Imipenem and meropenem	29 (65.9)	34 (32.4)	63 (42.3)	<0.001
Adequate antimicrobial therapy				
Within 3 days	17 (38.6)	56 (53.3)	73 (49.0)	0.10
Colistin	7/17 (41.2)	3/56 (5.4)		0.001

Table 1 continued

Characteristics	Number of patients (%) who died within 14 days (*n* = 44)	Number of patients (%) who survived within 14 days (*n* = 105)	Number of patients (%) who had PAB[a] or ABB[b] (*n* = 149)	*p* value
Non-colistin	10/17 (58.8)	53/56 (94.6)		
Within 7 days	18 (40.9)	74 (70.5)	92 (61.7)	0.001
Colistin	7/18 (38.9)	5/74 (6.8)		0.002
Non-colistin	11/18 (61.1)	69/74 (93.2)		

[a] *Pseudomonas aeruginosa* bacteremia

[b] *Acinetobacter baumannii* bacteremia

Table 2 Multivariate analysis of risk factors for 14-day mortality in patients with monomicrobial *P. aeruginosa* and *A. baumannii* bacteremia

Risk factors	Adjusted odds ratio (95 % CI)	*p* value
Model 1[a] (*n* = 149)		
ICU care within 1 month before bacteremia	4.45 (1.12–17.67)	0.034
Neutropenia <1 week before bacteremia	7.10 (1.45–34.68)	0.015
Heart failure	12.32 (1.02–148.50)	0.048
Charlson's comorbidity index score	1.67 (1.26–2.22)	<0.001
Pitt bacteremia score	1.43 (1.18–1.75)	<0.001
Model 2[b] (*n* = 139)		
Septic shock	7.02 (2.18–22.60)	0.001
ICU care within 1 month before bacteremia	10.91 (2.46–48.78)	0.002
Neutropenia <1 week before bacteremia	9.72 (1.42–66.46)	0.02
Charlson's comorbidity index score	1.80 (1.30–2.49)	<0.001
Adequate antimicrobial therapy within 3 days of bacteremia	0.23 (0.07–0.80)	0.02
Model 3[c] (*n* = 149)		
Septic shock	7.89 (2.52–24.66)	<0.001
ICU care within 1 month before bacteremia	9.62 (2.42–38.25)	0.001
Neutropenia <1 week before bacteremia	8.82 (1.34–58.19)	0.024
Charlson's comorbidity index score	1.78 (1.30–2.45)	<0.001
Type of antimicrobial therapy within 3 days of bacteremia		
Inadequate therapy	Reference	
Adequate colistin therapy	8.20 (1.07–62.90)	0.043
Adequate non-colistin therapy	0.22 (0.07–0.78)	0.019

[a] Including all study patients

[b] Excluding 10 patients who received colistin therapy within 3 days of bacteremia

[c] A risk factor of model 2, "adequate antimicrobial therapy within 3 days of bacteremia," was replaced by "type of antimicrobial therapy within 3 days of bacteremia"

There was no statistically significant difference in 14-day mortality between patients who received adequate monotherapy and those who received adequate combination therapy within 3 days of bacteremia (25.8 vs. 9.1 %, *p* = 0.44). A list of adequate antimicrobial agents used within 3 days of bacteremia and the 14-day mortality rates of patients are shown in Table 3.

Discussion

In 149 patients with monomicrobial PAB and ABB, 14-day mortality rate was 29.5 %. Adequate antimicrobial therapy within 3 days of bacteremia was not a preventive factor for 14-day mortality. However, when excluding patients who

Table 3 Adequate antimicrobial agents used within 3 days of monomicrobial *P. aeruginosa* and *A. baumannii* bacteremia by antibiotic class and 14-day mortality of patients who received each antimicrobial agent

Adequate antimicrobial agent within 3 days of bacteremia	Number of (%) patients ($n = 73$)	14-day mortality rate (%)
Monotherapy	62 (84.9)	16 (25.8)
Carbapenem	16 (21.9)	2 (12.5)
Ciprofloxacin or levofloxacin	17 (23.3)	1 (5.9)
Colistin	9 (12.3)	7 (77.8)
Ceftazidime or cefepime	8 (10.9)	5 (62.5)
Piperacillin/tazobactam	6 (8.2)	0
Aminoglycoside	3 (4.1)	0
Ceftriaxone	2 (2.7)	0
Tigecycline	1 (1.4)	1 (100)
Combination therapy	11 (15.1)	1 (9.1)
Ceftazidime/aminoglycoside	2 (2.7)	1 (50.0)
Piperacillin–tazobactam/ciprofloxacin	3 (4.1)	0
Ceftriaxone/aminoglycoside	2 (2.7)	0
Ciprofloxacin/aminoglycoside	2 (2.7)	0
Piperacillin–tazobactam/aminoglycoside	1 (1.4)	0
Meropenem/colistin	1 (1.4)	0

received colistin therapy within 3 days of bacteremia, it was a preventive factor.

Many studies have investigated the clinical impact of adequate antimicrobial therapy in patients with PAB or ABB, and the majority of these studies showed that early adequate antimicrobial therapy had a favorable impact on various clinical outcomes. However, some studies did not reveal any information on the receipt of colistin [3–9], some did not include any patients who received colistin [10–16], and some included only 1 or 2 patients who received colistin [17–19]. As a result, the clinical impact of adequate antimicrobial therapy for PAB or ABB has been rarely evaluated in more recent clinical situations that frequently necessitate colistin treatment. In our study, the favorable effect of early adequate antimicrobial therapy on 14-day mortality was lessened if patients receiving colistin therapy were included in the analysis. In one retrospective study including 13 patients receiving colistin, there was not an obvious preventive effect of early adequate antimicrobial therapy on mortality, although the data of patients receiving colistin were not described separately [20]. In our study, the decreased favorable impact of adequate antimicrobial therapy associated with colistin may be caused by a higher 14-day mortality rate of patients who received adequate colistin therapy than that of patients who received adequate non-colistin therapy (70.0 vs. 15.9 %, $p = 0.001$). The higher mortality may be the result of other factors, rather than the lack of effectiveness of colistin itself. In our study, patients receiving adequate colistin within 3 days of bacteremia more frequently had liver cirrhosis (20.0 vs. 1.6 %, $p = 0.048$), ICU care within

1 month before bacteremia (70.0 vs. 33.3 %, $p = 0.038$), carbapenem-resistant strains (70.0 vs. 9.5 %, $p < 0.001$), and more serious initial manifestations [mean Pitt bacteremia score (SD), 4.9 (3.4) vs. 1.9 (2.2), $p = 0.001$] than those receiving non-colistin antimicrobial agents. Perhaps related to these findings and the low number of study patients, even one of our multiple regression analyses showed that colistin was a risk factor for fatality. It is suggested that, as was described in a recent study, the need for colistin therapy, rather than colistin therapy itself, is associated with poorer survival [26]. However, insufficient effectiveness of colistin in patients with bacteremia has been suggested by a few studies. The well-known study by Falagas et al. [27], which showed the considerable effectiveness of colistin in 258 GNB-infected patients, suggested that colistin was more effective in the treatment of pneumonia rather than of bacteremia. Although the efficacy of colistin was suggested to be comparable to standard antimicrobial agents for ventilator-associated pneumonia in a recent meta-analysis [28], Paul et al. [26] reported that the adjusted odds ratio of colistin therapy for 30-day mortality was 1.99 (95 % CI = 1.06–3.77) in a subgroup of 220 patients with GNB bacteremia. Thus, further evaluation is necessary to investigate the effectiveness of colistin in patients with PAB or ABB, and more effective antimicrobial therapeutic strategies or new antimicrobial agents may be needed for patients with PAB or ABB.

This study has several important limitations. First, it is a retrospective cohort study. Especially, because of this nature of the study, there was no more detailed information on colistin therapy, such as actual time to initiation of

colistin or the application of initial loading dose of colistin. Second, the data of patients with monomicrobial PAB and those with ABB were combined for analysis because of the small sample size. Third, the number of patients receiving adequate colistin therapy was quite small ($n = 10$). In this point, our study may not provide strong evidence enough to identify any clinical impact of colistin. However, as described in the Introduction, previous studies of PAB or ABB rarely included patients receiving colistin therapy. Fourth, microbiological data such as colistin minimal inhibitory concentrations of the study organisms were not evaluated in our study.

In conclusion, the impact of early adequate antimicrobial therapy on the mortality of patients with monomicrobial PAB or ABB may be decreased in light of the common clinical practice of using colistin therapy. Further evaluation is needed to investigate the clinical impact of colistin in patients with PAB or ABB.

Conflict of interest The authors have no conflicts of interest to declare.

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