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ORIGINAL ARTICLE

Clinical response and outcome of pneumonia due to multi-drug resistant *Acinetobacter baumannii* in critically ill patients

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ABSTRACT

Background and Objectives: The frequency of multi-drug resistant *Acinetobacter spp*. infections is increasing in Iran. Considering availability of limited therapeutic options, clinical response and outcome of ventilator-associated pneumonia due to multi-drug resistant *A.baumannii* were evaluated in critically ill patients.

Materials and Methods: In this prospective study, 29 patients with carbapenem resistance *A. baumannii* ventilator-associated pneumonia were enrolled. Endotracheal aspirate specimens were analyzed according to the clinical and laboratory standard institute instructions in the hospital's microbiology laboratory. Demographics, clinical, microbiological and laboratory findings were collected for each patient during the treatment course. Therapeutic empirical regimen, change in antibiotic regimen following receiving antibiogram results, clinical and microbiological responses, duration of ICU stay and outcome were collected for each recruited individual.

Results: All of *A. baumanii* isolates were resistant to pipracillin-tazobactam, ceftriaxon, amikacin and ciprofloxacin. The resistance rate of *A. baumanii* species was 41.4% for ampicillin/sulbactabm and 93.1% for meropenem. Patients received either meropenem/colistin (51.7%) or meropenem/ampicillin-sulbactam (48.3%) as the treatment regimens based on the antimicrobial susceptibility patterns of isolates.

Ventilator-associated pneumonia clinical response, improvement and failure achieved in 15 (51.7%), 8 (27.6%) and 6 (20.7%) of the patients respectively. Microbiological eradication and intermediate status were observed in 9/29 (31%) and 11/29 (37.9%) of patients, respectively

Conclusion: The antibiotic regimens showed comparable efficacy in treatment of VAP due to MDR *A. baumannii* but mortality rate was high. Considering widespread and high mortality rates associated with MDR infections, applying infection control and antibiotic stewardship programs in hospitals are essential.

Keywords: *Acinetobacter baumannii,* Pneumonia, Antibiotic therapy, Clinical response

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INTRODUCTION

Acinetobacter baumannii is an aerobic Gram negative microorganism belonging to the *Moraxellaceae* family that emerged globally as a nosocomial pathogen in healthcare settings, especially in intensive care units (ICUs) (1). Multidrug-resistant (MDR) *A. baumannii* associated nosocomial infections have increased worldwide during two recent decades (1-3). Serious infections including blood stream, urinary tract, intra-abdominal and lower respiratory tract infections have been reported with this microorganism (1, 4). Despite applying preventive strategies, pneumonia continues to be number one complication in critically ill patients. Based on centers for disease control and prevention (CDC) report, pneumonia is the most common (21.82%) health care associated infection in acute care settings (3, 5). Infectious Disease Society of America (IDSA) has reported all-cause mortality related to ventilator associated pneumonia (VAP) up to 50% (3). *A. baumannii* is a predominant strain associated with VAP in most hospitals. This pathogen was the third common strains (approximately 5-10% of isolates) related to the VAP in the United States. The prevalence is higher in Asia than Europe and the United states (3). According to the CDC's National Healthcare Safety Network, about 2% of healthcare-associated infections are related to *Acinetobacter.* This prevalence is higher (approximately 7%) among critically ill patients requiring mechanical ventilation. On the other hand, up to 60% of the isolates were multidrug-resistant (MDR), and the mortality rate of these infections was about 7% (6).

The extensive use of antibiotics especially carbapenems for treatment of cephalosporin-resistant *Klebsiella spp* infections was detected as a main risk factor to emerge of carbapenem resistance strains, especially *Acinetobacter* (7, 8). The first carbapenem-resistant *A. baumannii* nosocomial outbreak was reported in the United States in 1991. After that, several outbreaks of carbapenem-resistant *A. baumannii* infections were detected in many hospitals in various geographic areas (9-11). These infections are associated with increased mortality and morbidity, length of hospital stay, and clinical costs (4, 12).

Limited antibiotic regimens are available for treatment of carbapenem resistance *Acinetobacter spp.* infections (11). Older agents, including ampicillin/sulbactam, carbapenems and colistin remain the last therapeutic options for treatment of the infections in developing countries. Combination therapy is a common strategy against MDR infections (13). The antimicrobial synergistic effect between meropenem, ampicillin/sulbactam and colistin has been reported in some studies. This effect was detected despite in-vitro resistance to both antibiotics (13, 14).

The frequency of MDR *Acinetobacter spp.* infections is increasing in Iran (15). Considering availability of limited therapeutic options, clinical response and outcome of VAP due to MDR *A. baumannii* were evaluated in critically ill patients.

METHOD

This was a prospective study that conducted over a period of eight months, from October 2015 to May 2016 at Imam Khomeini Complex Hospital, a referral teaching hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. In This study, 29 patients with ventilator-associated carbapenem resistance *A. baumannii* pneumonia were enrolled. These patients were admitted in ICU and experienced mechanical ventilation for more than 48 hours before the onset of infection. VAP was defined according to the imaging, clinical and laboratory findings (Table 1). New or progressive infiltration in chest x-ray with at least two of following parameters including fever (T>38°C) or hypothermia (T<35.5°C), leukocytosis (WBC>12000 cells/ml) or leukopenia (WBC<4000 cells/ml) or positive tracheal culture, were used for pneumonia diagnosis (16, 17). Endotracheal aspirate specimens were analyzed according to the clinical and laboratory standard institute (CLSI) instructions in the hospital's microbiology laboratory. Routine microbiological techniques were used for culture, isolation and differentiation of microorganisms (18). *A. baumannii* isolates were selected for follow-up and further analysis. Antibiotic disks including ampicillin/sulbactam (10/10 µg), ceftriaxone (30 µg), imipenem (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), trimethoprim-sulfamethoxazole (1.25/23.75µg) were applied to determine *A. baumannii* susceptibility pattern based on the CLSI recommendations (18). These antibiotic disks were applied on Muller-Hinton agar containing colony suspension of *A. baumannii* equivalent to a 0.5 McFarland standard sample. If an isolate of *A. baumannii* was resistance to more than one

Table 1. Criteria for diagnosis of ventilator-associate pneumonia (16-17)

Radiology	Sign/Symptom	Laboratory
At least one of the following findings in serial chest radiography: -New or progressive and persistent infiltrate -Consolidation -Cavitation	At least one of the following signs or symptoms: -Fever (>38°C) -Leukopenia (<4000 WBC/mm^3) or leukocytosis (>12000 WBC/mm^3) **and** At least one of the following: -Sputum production or change in antecedent sputum characteristics (including consistency, colure or quantity) or increased respiratory secretions or suctioning requirements -New onset or worsening of antecedent cough, dyspnea or tachypnea -Abnormal respiratory sounds -Worsening gas exchange including hypoxia, hypoxemia, increased requirement for oxygen support or mechanical ventilation	At least one of the following: 1. Positive blood culture originated from respiratory tract 2. Positive pleural fluid culture 3. Positive culture of respiratory tract sample (endotracheal aspirate secretions)

agent in ≥3 antimicrobial categories including aminoglycosides, carbapenems, fluoroquinolones, β-alactam-β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, tetracyclines and polymyxins, it was considered as MDR microorganism and were recruited in our study (2). Demographics, clinical, microbiological and laboratory findings were collected for each patient during the VAP treatment course. Comorbidities and illness severity were assessed according to the Charlson comorbidity score. Therapeutic empirical regimen, change in antibiotic regimen following receiving antibiogram results, clinical and microbiological responses, duration of ICU stay and outcome were collected for each recruited individual. Incompatible isolates with patients' clinical status were considered colonization and were excluded. Clinical and microbiological responses were used to assess efficacy of the antibiotic regimens. Clinical response was considered when patient's general condition, oxygenation status, and laboratory findings improved following antibiotic therapy. Microbiological response was defined as eradication, intermediate, super-infection and persistent at the end of treatment (19). The nephrotoxicity was compared between the regimens based on the Kidney Disease Improving Global Outcome (KDIGO) recommendation. Based on the definition, an increase in serum creatinine by 0.3 mg/dl within 48 h or an increase in serum creatinine to ≥ 1.5 times of baseline within the previous 7 days or urine volume ≤ 0.5 ml/kg/h for 6 h was considered as drug-induced acute kidney injury (20).

Continuous and categorical variables were reported as mean± standard deviation and numbers or percentages, respectively. Mann-Whitney Rank Sum test was performed to compare the duration of ICU stay in the treatment groups. Fisher's Chi-square tests were used for the assessment of clinical responses. Statistical Package for Social Sciences (SPSS) 21.0 statistics program was used for data analysis and P-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 871 patients were ad-

mitted in the ICU. A total of 116 (13.32%) out of 871 patients were developed VAP during ICU stay. VAP due to MDR *A. baumanii* was detected in 32 (3.67%) patients. Three patients were excluded from the study because of prior VAP episodes or expired less than 48 h of the treatment. In this period, 116 endotracheal aspirate specimens were analyzed in the hospital's microbiology laboratory. Totally, 48 isolates (60.76%) were identified as *A. baumannii* and the remaining were *Klebsiella spp.*, 17 (21.52%), *Pseudomonas aeruginosa,* 9 (11.39%), *Staphylococcus aureus,* 2 (2.53%), *E. coli*, 1 (1.26%), *Staphylococcus epidermidis,* 1 (1.26%) and *Streptococcus viridians,* 1 (1.26%). Culture positive and negative pneumonia were detected in 79 (68.1%) patients and others (n=37, 31.9%) were considered as culture negative pneumonia. The mean age of the patients was 59.21±19.42 years old and 20 (69%) of them were males.

The calculated Charlson comorbidity score, underlying diseases and clinical features of patients were shown in Table 2. The mean±SD of Charlson comorbidity score was 3.53±1.96 (10-year survival percentage was from 53.39% to 77.48%).

Early VAP was detected within the first four days of ICU admission in 25.9% of patients. All of *A. baumannii* isolates were resistance to pipracillin-tazobactam, ceftriaxon, amikacin and ciprofloxacin. The

Table 2. Clinical characteristics and underlying diseases of patients

Patient's characteristics	Number (%) or mean±SD	
Gender		
Female	8 (31)	
Male	20 (69)	
Age	59.21±19.42	
WBC and vital sign:	Before treatment	After treatment
WBC(x 10^3 per µL)	14.34±5.42	9.49±3.72
HR(*beats* per minute)	103.37±20.04	96.27±19.9
RR (breaths per minute)	22.21±7.06	15.39±3.52
MAP (mmHg)	88.92±16.55	87.09±11.38
T (°C)	37.87±1.15	37.11±0.52
Charlson comorbidity score	3.83±2.71	
DM	7 (24.13%)	
CHF	1(3.45%)	
IHD	4 (13.79%)	
HTN	8 (27.59%)	
COPD	7 (24.13%)	
CKD	1(3.45%)	
CVA	2 (6.9%)	
Parkinson	3(10.34%)	
Alzheimer disease	1(3.45%)	
Solid tumor		
Non-metastatic	5 (17.24%)	
Metastatic	2 (6.9%)	
Thyroid disorder	1 (3.45%)	
CIDP	1 (3.45%)	

DM, diabetes mellitus; CHF, chronic heart failure; IHD, ischemic heart disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CIDP, chronic inflammatory demyeliniating polyneuropathy; WBC, white blood cell; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; T, temperature.

resistance rate of *A. baumannii* species was 41.4% for ampicillin/sulbactabm and 93.1% for meropenem. Antimicrobial sensitivity pattern of *A. baumannii* isolates was reported in Table 3. Patients received either meropenem/colistin (51.7%) or meropenem/ampicillin-sulbactam (48.3%) as the treatment regimens based on the antimicrobial susceptibility patterns of isolates.

Mean duration of VAP treatment and ICU stay of patients were 13.41±5.53 and 40.34±28.90 days respectively. There was not any significant difference in the duration of ICU stay between the groups. VAP clinical response, improvement and failure achieved in 15 (51.7%), 8 (27.6%) and 6 (20.7%) of the patients respectively. Microbiological eradication and intermediate status were observed in 9/29 (31%) and 11/29 (37.9%) of patients, respectively. *A. baumannii* was persisted in 3/29 of patients (10.3%) and the rate of super-infection on the follow-up culture was 6/29 (20.7%). *Klebsiella spp.* (66.7%) was the most common microorganism of super-infections followed by *P. aeruginosa* (33.3%).

Clinical failure occurred in 3/15 (20%) and 3/14 (21.40%) of patients who received meropenem/colistin and meropenem/ampicillin-sulbactam respectively. No significant difference was observed between the regimens regarding clinical failure. Colistin-induced nephrotoxicity was detected in 2/15 (13.33%) patients. Ampicillin-sulbactam associated nephrotoxicity was not observed in any patient. Finally, 12/29 (41.4%) of the individuals were discharged from the hospital and 17/29 (58.6%) patients died. The characteristics of our patients are summarized in Table 4.

DISCUSSION

In this study, the antibiotic regimens showed similar efficacy in the treatment of VAP due to MDR *A. baumannii.* Both clinical and microbiological responses, duration of ICU stay and nephrotoxicity were comparable between the treatments.

Considering the geographic area, setting and population, different incidence rates of VAP have been detected (22-23). Incidence of VAP was reported between 1.9 and 18.3 cases per1000 ventilator-days around the world (21). Incidence of VAP due to *A. baumannii* was reported about 1.59 cases per 100 CCU admissions in one study (22).

In a large multi-center study that covered 27 ICUs in nine European countries, 30.5% of nosocomial pneumonia were culture negative. Approximately one from three tracheal discharge cultures was negative in our study that was comparable with the previous reports. In culture positive nosocomial pneumonia, *Enterobacteriaceae, S. aureus, P. aeruginosa,* and *A. baumannii* were common isolates respectively. *A. baumannii* was more frequent in patients with late than early VAP (21). Unfortunately, MDR *A. baumannii,* was the most prevalent pathogen in our study.

According to the CDC's report, carbapenem resistance rate of *A. baumannii* clinically increased from 9% to 40% during 1995-2004 (23). Approximately 27.3% of *A. baumannii* isolates from tracheal samples were considered as MDR pathogens in a prospective study from North India (24). Same finding was detected in our patients. All *A. baumannii* strains were resistant to ceftriaxone and ciprofloxacin, and the resistance rate to imipenem and colistin was 0.09% and 0%, respectively (22). In a retrospective cohort study in Greece, all *A. baumannii* isolates were resistant to carbapenems and aminoglycosides, and 93.5% of these strains were susceptible to colistin (25).

Multiple antibiotic regimens were examined for treatment of infections due to MDR *A. baumannii* (26, 27). Combination therapy including a carbapenem and another effective antibiotic was more effective

Table 3. Antimicrobial susceptibilitypattern of *A. baumanii* isolates

Antimicrobial agents	Sensitive	Intermediate	Resistance
3th-generation cephalosporins	-	-	100%
Ciprofloxacin	-	-	100%
Ampicillin-sulbactam	44.8%	13.8%	41.4%
Piperacillin-tazobactam	-	-	100%
Aminoglycosides	-	-	100%
Carbapenems	-	6.9%	93.1%

Table 4. Characteristics of included patients in summary

No	Age	Gender	Baseline disease	Treatment regimen	Duration of ICU stay (day)	Microbiological response	Clinical response	Outcome
1	31	F	CIDP[a]	Meropenem/ampicillin-sulbactam	32	Persistent	Cure	EXP.
2	82	F	-	Meropenem/ampicillin-sulbactam	96	Persistent	Improvement	DC.
3	32	F	Cerebral hemangio-blastoma	Meropenem/colistin	10	Eradication	Cure	DC
4	32	F	Metastatic breast cancer	Meropenem/ampicillin-sulbactam	105	Eradication	Improvement	EXP
5	51	M	Metastatic spinal tumor	Meropenem/ampicillin-sulbactam	47	Eradication	Cure	DC
6	53	M	Ankylosing Spondylitis	Meropenem/ampicillin-sulbactam	35	Super-infection	Improvement	EXP.
7	60	M	Gastric cancer	Meropenem/colistin	22	Intermediate	Failure	EXP.
8	65	M	CVA, HTN, Parkinson	Meropenem/colistin	49	Eradication	Cure	DC
9	79	F	HTN	Meropenem/colistin	69	Intermediate	Cure	EXP.
10	45	M	-	Meropenem/ampicillin-sulbactam	10	Intermediate	Failure	EXP.
11	49	M	IHD, DM, HTN, CVA	Meropenem/ampicillin-sulbactam	61	Intermediate	Failure	EXP.
12	65	M	IHD, CABG, DM, HTN, BPH	Meropenem/colistin	82	Eradication	Cure	DC.
13	73	M	-	Meropenem/ampicillin-sulbactam	10	Intermediate	Cure	DC.
14	79	M M	IHD, DM, CKD, CVA, Rectal carcinoma	Meropenem/ampicillin-sulbactam		Super-infection	Cure	
15	65	M	Prostatic adenocarci-noma	Meropenem/ampicillin-sulbactam	39	Superinfection	Improvement	EXP.
16	80	M	CHF, MI, COPD, Alz-heimer disease	Meropenem/colistin	84	Intermediate	Cure	EXP.
17	60	M	Lung transplantation	Meropenem/colistin	17	Supe-rinfection	Failure	EXP.
18	84	F	CABG, Valvular AF, COPD	Meropenem/colistin	19	Super-infection	Failure	EXP.
19	41	F	Parkinson	Meropenem/ampicillin-sulbactam		Eradication	Cure	DC.
20	67	F	CVA	Meropenem/colistin	12	Super-infection	Improvement	EXP.
21	85	M	HTN, IHD, DM, CVA	Meropenem/colistin	55	Eradication	Cure	EXP.
22	70	M	HTN, DM, BPH, hypo-thyroidism	Meropenem/colistin	31	Intermediate	Improvement	EXP.
23	75	M	DM, CVA	Meropenem/ampicillin-sulbactam	40	Intermediate	Improvement	DC.
24	76	M	HTN, Parkinson	Meropenem/colistin	34	Intermediate	Improvement	EXP.
25	68	M	Rectal carcinoma	Meropenem/ampicillin-sulbactam	13	Intermediate	Failure	EXP.
26	23	M	Down syndrome	Meropenem/ampicillin-sulbactam	93	Eradication	Cure	DC.
27	17	F	-	Meropenem/colistin	12	Intermediate	Cure	DC.
28	68	M	HTN, DM, CVA	Meropenem/colistin	32	Persistent	Cure	EXP.
29	41		-	Meropenem/colistin	11	Eradication	Cure	DC.

DM, diabetes mellitus; CHD, chronic heart disease; IHD, ischemic heart disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CIDP, chronic inflammatory demyelinating polyneuropathy; MI, myocardial ischemia; CABG, coronary artery bypass graft; BPH, benign prostatic hyperplasia; EXP, expired; DC, discharged.

than monotherapy for MDR *A. baumannii* associated pneumonia. Synergistic effect of carbapenems with other antimicrobial agents against *A. baumannii* infections was proposed (27). In another study, clinical and microbiological responses were higher in colistin plus a carbapenem than sulbactam plus colistin or colistin alone (28).

The efficacy of sulbactam in treatment of *A. baumannii* related infections has been reviewed (27, 29, 30). Betrosian et al. evaluated the efficacy of high-dose regimens of ampicillin/sulbactam (18/9 g versus 24/12 g daily dose) for treatment of VAP due to MDR *A. baumannii.* No significant difference in clinical response was noted between the groups (19). Clinical response rate in this study for both regimens was up to 75% (27). Efficacy of regimens containing ampicillin/sulbactam was similar in our study.

Synergistic effect of a carbapenem and ampicillin/sulbactam for treatment of MDR *A. baumannii* infections in critically ill patients was reported. In one study, treatment of VAP due to carbapenem-resistance *A. baumannii* with ampiclin/sulbactam or colistin had similar clinical response. However, the microbiological response was higher in colistin group (29). In another study clinical resolution of pneumonia due to carbapenem-resistance *A. baumannii* was detected in 67.6% of patients treated with sulbactam or ampicillin/sulbactam (27).

Increase in serum creatinine level among patients who received colistin for treatment of VAP was more common than other therapeutic regimens (29). Colistin associated nephrotoxicity was reported from 0 to 57%. Receiving concurrent nephrotoxic agents and some patient's characteristics (advanced age, obesity, baseline kidney disease, lower serum albumin, higher Charlson comorbidity score), different methods of colistin dosing and the criteria used for detection of nephrotoxixity may be attributed for this variability (31). Both patients with colistin-induced nephrotoxicity in our study were in old age and one of them suffered from chronic kidney disease.

Mortality rate (28.57%) of VAP due to MDR *A. baumannii* in our study was comparable to other studies. Attributed mortality of *A. baumannii* infections was reviewed in multiple studies. The differentiation between VAP-related and all-cause mortality in critically ill patient is difficult. (21, 29, 32, 33). The mortality rate related to nosocomial pneumonia was reported as 19.6% in European ICUs (21). Patients with nosocomial pneumonia had 6% higher mortality rate than other complications (21). In a systematic review, the mortality rates of hospital and ICU-associated *A. baumannii* infections were 7.8% to 23% and 10% to 43% respectively (33). In another study, 30 day mortality rate of pneumonic due to *A. baumannii* was 31.2%. Mortality rate of pneumonia associated with *A. baumannii* was different considering the therapeutic regimens. The outcome of VAP caused by carbapenem-resistant *A. baumannii* which treated by either ampicillin/sulbactam or colistin was evaluated in one study. Colistin regimen was associated with higher rate of 30 day mortality than ampicillin/sulbactam treatment (29). However, in a prospective study, mortality rate of *A. baumannii* associated pneumonia did not differ significantly between colistin and ampicillin/sulbactam regimens (34).

Malignancy, kidney and liver diseases, immune-compromised status, septic shock, late-onset VAP, high SOFA score, drug-resistant pathogens, and inappropriate antibiotic treatments were detected as prognostic factors for *A. baumannii* related mortality in critically ill patients (32).

These evidences support comparable clinical and microbiological responses of sulbactam (ampicillin/sulbactam) and colistin for treatment of MDR *A. baumannii* infections in critically ill patients. Besides clinical response, safety, collateral damage and cost are other important parameters in selecting appropriate antibiotic regimens, especially in critically ill patients with concomitant diseases and organs failure. Colistin is known as a nephrotoxic agent and for many years, its administration had been restricted. Following emerging of MDR pathogens and unavailability of effective treatments, colistin is re-introduced in clinical practice. Fortunately, its nephrotoxicity is less than that was suspected (35-36).

Colistin and sulbactam are narrow spectrum antibiotics and always cover Gram-negative microorganisms. However, ampicillin-sulbactam has broad antibacterial activity against Gram negative and positive microorganisms and even anaerobes. Collateral damage and increasing rate of colonization with resistant pathogens are critical concerns regarding use of broad-spectrum antibiotics (37-38). Effectiveness of ampicillin-sulbactam against *A. baumannii* is related to sulbactam component (30), therefore availability of this agent as a unique formulation in developing countries can limits use of ampicillin-sulbactam. In our country, colistin is more expensive than ampicillin-sulbactam.

Although this is first case series that reports clinical response and outcome in Iranian critically ill patients with VAP due to MDR *A. baumannii* but our report suffers from some limitations. Different patients' demographic characteristics and baseline diseases, small sample size, and duration of follow-up were main restrictions. Most of recruited patients had severe comorbidities including malignancies, respiratory disorders, ischemic heart disease, heart failure, diabetes mellitus, renal failure, cerebrovascular accident and sepsis. High mortality rate among our patients may be related to these conditions. Efficacy and safety of antibiotic regimens for treatment of *A. baumannii* infections were evaluated in few studies. Well-designed and multi-center studies with adequate sample size are needed to clarify the best antibiotic regimen for treatment of these infections.

CONCLUSION

Although colistin and ampicillin-sulbactam containing antibiotic regimens showed comparable efficacy in treatment of VAP due to MDR *A. baumannii* in our patients but mortality rate, was high. Considering widespread and high mortality rates of MDR infections, applying infection control and antibiotic stewardship programs in hospitals are essential.

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