Colistin resistance in *Acinetobacter baumannii* isolated from critically ill patients: clinical characteristics, antimicrobial susceptibility and outcome

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Abstract:

Background: *Acinetobacter baumannii* (AB) is increasingly becoming a clinically relevant organism due to the rising number of associated nosocomial infections. The therapeutic options are extremely minimal because of its ability to develop resistance to all available antimicrobials, including colistin (CST). Data on the clinical and microbiological characteristics of colistin-resistant *A. baumannii* infections remain scarce to date.

Methods: In this prospective study, clinical isolates of colistin resistance among *Acinetobacter* strain was evaluated from the database of Microbiology Laboratory of King Khalid University Hospital, Saudi Arabia.

Results: In a total of 142 patients with 136 *Acinetobacter* isolates, *Acintobacter baumannii* was the predominant serotype 73% of the isolates and *Acinetobacter lwoffii* constituted 27% of the isolate .There was 8.5% colistin resistant isolates with colistin E-test MIC >4. The clinical characteristics were determined for colistin resistant *Acinetobacter baumannii.* All patients were critically ill and 64% of them were hositalized in the Intensive Care Unit (ICU). All patients have been previously given antibiotics. Other associated clinical characteristics included; morbid obesity and sleeve gastrectomy (21 %), mechanical ventilation and central venous catheter (50%). High mortality rate was found(28%).

Conclusion: There is an increase of colistin resistance among clinical isolates of *Acinetobacter baumannii* causing serious infections especially in critically ill patients.

Keywords: *Acinetobacter baumannii*, colistin resistance, clinical characteristics.

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Introduction

Acinetobacter baumannii (AB) is one of the important multidrug resistant Gram-Negative nosocomial pathogens. It is responsible for many serious infections such as pneumonia, sepsis, urinary tract and wound infections.[1] Multiple factors lead to colonization with *Acinetobacter baumannii*, such as prolonged hospital stay, post- surgical procedures, ICUadmission and prior treatment with broad spectrum antibiotics.[2,3] Recently, *Acinetobacter* strains exhibited elevated rates of carbapenem resistance (as high as 58%).[4] Colistin, a natural substance produced by *Bacillus polymyxa* and a cationic lipopeptide (cyclic decapeptide) was discovered in 1949. Colistin was considered as one of the last therapeutic options for treatment of the multiresistant *Acinetobacter baumannii* infection.[5] It has been recommended for the treatment of ventilator associated pneumonia caused by drug resistant gram negative organism.[6] Recently colistin has been used as rescue therapy for severe infection.[7] However, resistance to colistin has recently been described worldwide.[8-12] Few data on *Acinetobacter* spp. infection and colistin resistance in Saudi Arabia is currently found in the literature.[13,14] The objectives of the present study were to evaluate the clinical characteristics, antimicrobial susceptibility testing and outcomes of patients infected with colistin-resistant *Acinetobacter baumannii*.

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Methods

Study design

This study was a prospective review conducted in a teaching hospital located in Riyadh, Saudi Arabia using the Microbiology Laboratory database and the daily patients' records from February 2015 through April 2016.

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Bacterial isolates

A total of 136 non-duplicate clinical isolates of *Acinetobacter* isolates obtained from 142 patients, of which 14 patients had multiple infections with different *Acinetobacter* species. Various specimens were collected from different sites including blood, genitourinary tract, respiratory tract and wounds specimens. Multidrug resistant bacteria are described as being resistant to at least one agent in three or more antibiotic categories.

Antimicrobial susceptibility testing

The identification of the isolates and colistin susceptibility testing were performed by Vitek 2 (bioMérieux, France), and the colistin-resistant MICs were confirmed by E test methods, according to CLSI recommendations.[15] The E test method was previously validated on the microbiology laboratory using broth microdilution (Trek Diagnostics Systems), according to CLSI recommendations.[15] The susceptibility categories were interpreted according to break-points of CLSI guidelines.[16] for non-fermentative isolates and EUCAST.[17] for *Enterobacteriaceae* members. Colistin minimum inhibitory concentrations (MICs) >2 μg/mL were considered resistant.[18]

Patient's clinical data

The clinical characteristics associated with acquiring multiresistant *Acinetobacter baumannii* were determined by reviewing the clinical data recorded in the patient's medical chart.

Results

Characteristics of isolates

Of the 227 *Acinetobacter* isolates obtained from (142) patient, 64 duplicate isolates were excluded. Total of 163 *Acinetobacter* isolates were included and 10% (14/142) had more than one site of infection. Almost 41.8% (68/163) of the *Acinetobacter* isolates were multidrug resistant. Over the study period, the prevalence of monthly reported *Acinetobacter* spp. was recorded in the data base of the Microbiology laboratory and it was steadily increasing reaching the highest prevalence (30%) of the total 136 *Acinetobacter* isolates which was observed in March (2016) [Figure 1].

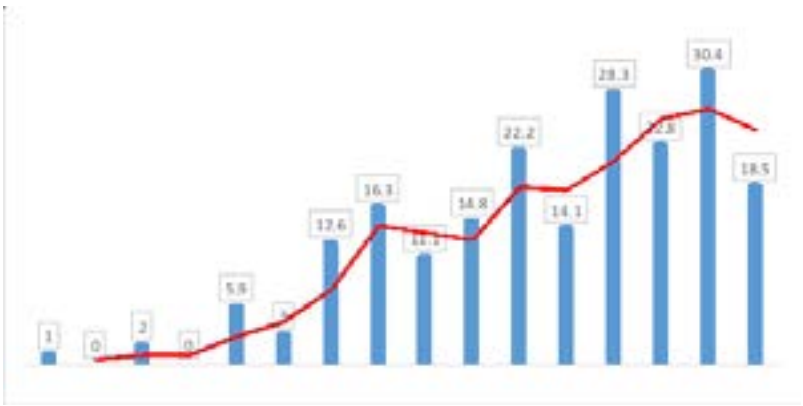


Figure 1: Prevalence of 136 Acinetobacter species isolates over the study period

Acinetobacter baumannii isolates 119 (73%) were the most common identified isolates of all *Acinetobacter species*. Fourteen *Acinetobacter baumannii* isolates (14/163, (8.6%) were colistin resistant, (MIC: ≥ 4 mg/ml).

Site of infection

The most common sites of specimens included respiratory tract (6/14; 42%), urine (2/14; 14%), wound (1/14; 7%), blood (4/14; 28%), and tissue (1/14; 7%).

Clinical and demographics of patients

Demographic data and associated clinical characteristics and comorbid diseases that were more prevalent in the 14 patients infected with colistin resistant *Acinetobacter baumannii* are illustrated in [Table 1].

Table 1. Clinical characteristics of patients infected with colistin resistant *Acinetobacter baumannii*

Clinical characteristics	n=14	%
Age (mean)	12yr-91yr.	
Gender		
- Male	9	63
- Female	5	41
Admission		
- ICU	9	64
- Medical	6	43
- Surgical	3	21
Medical/Surgical Comorbidity:		
- Diabetes mellitus	4	28
- Hypertension	4	28
- Morbid Obesity	3	21
- Chronic renal failure	3	21
- Heart disease	4	28
- Malignancy	2	14
- Immunosuppression	1	7
- Septic shock	2	14
- Surgery	5	35
- Sleeve Gastrectomy	3	21
Hospitalization (last 3 months)	7	50
Invasive devices		
- Mechanical ventilation	7	50
- Central venous catheter	7	50
- Urinary catheter	5	35
Death	4	28

ICU; Intensive Care Unit

Of the 14 patients between the age of (12-91), there were 9 male (64%) and 5 females (35%) and one pediatric patient (7%) who had lymphoma. Nine patients were admitted in the intensive care unit (64%). Four (28%) patients had diabetes mellitus and hypertension. chronic renal failure, morbid obesity, and sleeve gastrectomy were identified in 3 patients (21%) respectively. Sleeve gastrectomy was done one year, seven months and three months prior to the study in three patients. Seven (50%) patients were mechanically ventilated. Central line and urinary catheter were used in (50%,43%) respectively. Prior hospitalization was documented in all *A. baumannii* colistin resistant infected patients(100%). All patients received antibiotics before the diagnosis of AB infection including carbapenem (78.5%) colistin (28%), vancomycin (64%), tazocin (50%), linezolid (14%), aminoglycoside (14%) and antifungal agents (43%). High mortality rate (28%) was found among patients with AB colistin resistant infection in spite of intensive treatment. Treatment of patients included colistin in combination with aminoglycosides or carbapenem. Data obtained after analyzing resistance to AB strains isolated showed that this bacteria's antibiotic resistance was high. The Minimum Inhibitory Concentration (MIC) of colistin against the various *Acinetobacter baumannii* for which the MIC E-test was performed is presented in [Table 2].

Table 2. Previous antibiotics used for the last 3 months in patients with *Acinetobacter baumannii* infection

Antibiotic	N	%
- Total	14	100
- Colistin	5	35
- Carbapenem	10	71
- Glycopeptide (vancomycin)	9	64
- Cephalosporin	3	21
- Aminoglycoside	2	14
- Quinolone	0	0
- Piperacillin-tazobactam	7	50
- Linezolide/daptomycine	2	14
- Tigecycline	1	7
- Metronidazole	2	16
- Antifungal	6	43

Discussion

In this study the prevalence of *Acinetobacter* isolates was found to be steadily increasing. This finding was reported by other studies; a study from Iran showed that, the prevalence of drug resistance among the clinical samples of *A.baumannii* isolated against most of the antibiotics is very high.[19] Another study from Romania has shown that a large number of *A. baumannii* strains were resistant to the tested antibiotics. The lowest resistance was recorded for ampicillin and sulbactam and the highest resistance rate was recorded for ceftazidime and imipenem.[20-24]

Acinetobacter baumannii isolates were the most common identified isolates of all *Acinetobacter* species, (73%) this finding was similar to other studies.[25,26]

In this study a large number of colistin-resistant/carbapenem-resistant *A. baumannii* was observed. Similar to our finding, the emergence of colistin resistant *A. baumannii* has been observed in several countries.[27-30]

A study from Central Greece showed a significant increase of colistin-resistant/carbapenem-resistant *A. baumaniias* a total of 86 colistin-resistant/carbapenem-resistant out of 1228 *A. baumannii* were collected between 2012 and 2014.[31]

The age of the patients was variable between 4-90 years; all of them were critically ill and had chronic disease such as hypertension, chronic renal failue, morbid obesity and malignancy. All of them had prior hospital admission and were treated with different antibiotics including carbapenem, aminoglycoside and vancomycin. More than 50% of the patients required central line and urinary catheters.

Knowledge of these possible risk factors for Colistin-resistant *A. baumannii* is a challenge for antibiotic treatment and infection control policies. We found that the majority of the patients were admitted in the intensive care unit (64%). Mechanical ventilation in (50%), Prior hospital admission and antibiotic use were documented in all patients (100%). Similar findings were reported by Qureshi et al; in his study all patients but one were in the ICU at the time of isolation of colistin- resistant *A. baumannii* and (65%) of the patient used ventilator.[32]

In this study, among the antibiotics that had been used previously carbapenem was used in (78.5%) of the patients, while colistin was used in (28%). In Qureshi et al study,95% of the patients had received intravenous and/or inhaled colistin for the treatment of carbapenem-resistant, colistin-susceptible *A. baumannii* infection prior to identification of colistin-resistant isolates.[32]

Another study from Turkey reported that previous quinolone use in the last three months (P=.003; RR:3.2; 95% CI:1.5-6,7) and previous colistin use in the last three months (P=.001; RR: 3.6; 95% CI: 1.63-7.99) were significant risk factors in the multivariate analysis associated with infection by colistin-resistant microorganisms.[33]

In spite of intensive treatment, 28% of our patients died by 30 days. A study from USA reported high mortality rates among almost all patients with colistin resistance AB and suffering from ventilator-associated pneumoniae.[32] Another study from Brazil reported 7 out of 20 isolates were colistin resistant and 8 patients died during therapy.[34]

A retrospective cohort study was conducted in the medical/surgical ICU at Zhongshan Hospital in Shanghai, China. Adult patients meeting the criteria of *A.baumannii* VAP from January 2012 to October 2015 were enrolled. Seventy-eight patients were included in this study. The 30-day mortality rate in ICU for the patients was 37.2%.[35] We believe that this is a high mortality rate in comprasion to our study where the mortality rate was (28%).

To our knowledge, our study involved 14 unique patients with infection due to colistin-resistant AB.

The most important limitation of this study was that it was of a small number of samples, probably because it was a prospective study that was carried out in relatively short time. Despite all limitations, this study represents the largest series describing clinical characteristics of colistin-resistant AB. Our data highlights an emerging clinical problem. Hence, early detection and optimization of infection control practices are required.

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Conflict of interest

None declared.

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