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Impact of Carbapenem Resistance on Clinical Outcomes in Acinetobacter baumannii Infections: A Tertiary Care Hospital Study

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Abstract

Background: Acinetobacter baumannii has emerged as an opportunistic pathogen associated with health care associated infections. Carbapenem-Resistant Acinetobacter baumannii (CRAB) is considered as "Priority 1: Critical" pathogen. This study evaluated the predisposing factors and clinical outcomes associated with infections caused by CRAB.
Methods: Clinically relevant A. baumannii isolated from various clinical specimens were considered. Isolates were classified as Carbapenem Resistant Acinetobacter baumannii (CRAB) and Carbapenem Susceptible Acinetobacter baumannii (CSAB) based on CLSI interpretive criteria. Clinical data were obtained by reviewing medical records. Data was analysed using SPSS Version 25. A p value < 0.05 was considered statistically significant.
Results: A total of 95 clinically significant isolates of A. baumannii were analysed, of which 50 (52.6%) were carbapenem resistant. Majority of isolates were recovered from respiratory specimens. The mean age of patients with CRAB infections were significantly higher (65.86 ± 10.57) than those with infection with carbapenem sensitive strains (55.3 ± 24.74). Diabetes mellitus, hypertension, and underlying respiratory diseases were other significant predisposing factors in patients with CRAB infections. Presence of indwelling medical devices were not significantly associated with infection by carbapenem resistant strains. Empirical antibiotic therapy was not appropriate in most of the patients with CRAB infections. Duration of ICU and hospital stay were significantly longer when compared to those with infections with carbapenem sensitive strains. Mortality rates were also significantly higher among patients with CRAB infections (64% vs 40%).
Conclusion: Carbapenem resistance in Acinetobacter baumannii is associated with delayed appropriate therapy, prolonged hospitalization, and significantly higher mortality. Strengthening antimicrobial stewardship, early identification of resistant pathogens, and strict infection prevention and control measures are essential to limit the emergence and spread of CRAB in hospital settings.

Keywords: CRAB, Healthcare-associated infections, Antimicrobial stewardship

INTRODUCTION

Acinetobacter baumanii is a saprophytic gram negative bacilli found abundantly in soil and water. Given its ability to survive on dry surfaces for months and thrive in various adverse conditions[(1)], it has emerged as an opportunistic pathogen to the vulnerable hospitalized population[(2)]. As they can easily colonise hospital environments and medical equipments[(3)], they are associated with all sorts of health care associated infections under surveillance, particularly the device associated ones like ventilator associated pneumonia, central line associated blood stream infections and catheter associated urinary tract infections[(2)].

The clinical significance of *Acinetobacter baumannii* is further enhanced by its distinct property to demonstrate multiple antimicrobial resistant properties, ranging from upregulated expression of chromosomally encoded genes and horizontal acquisition of novel genetic determinants. Because of its multidrug resistant nature, Carbapenems was considered as the first line treatment choice for infection by this organism. However under selective pressure, carbapenem resistant strains are emerging and are subsequently spreading globally. Resistance here is mainly due to the production of OXA type carbapenemase[(4)] along with other mechanisms like porin loss, efflux pump overexpression, and mutations in antibiotic targets[(5)].

Several studies have shown that Carbapenem-Resistant Acinetobacter baumannii (CRAB) infections are associated with increased mortality rates. World Health Organization (WHO) has classified CRAB as "Priority 1: Critical" pathogen[(4)]. Currently, polymyxins, specifically colistin serve as the final therapeutic line for CRAB infection[(6)]. However colistin resistant strains are also emerging[(7)].

In view of the growing burden of antimicrobial resistance and the clinical challenges associated with CRAB infections, this study was conducted to evaluate the

predisposing factors and clinical outcomes associated with infections caused by CRAB.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted in a tertiary care teaching hospital in South Kerala after obtaining Institutional Ethics Committee clearance (PIMSRC/E1/388A/54/2024).

Minimum sample size of 94 was calculated based on previous study done in our hospital where prevalence of Carbapenem resistant A. baumanii was 41.3%. Only clinically relevant A. baumannii isolated from various clinical specimens were considered. Infections where A. baumannii was isolated along with other organisms, were excluded from the study to avoid confounding factors while assessing the clinical significance of various factors attributed specifically to A. baumannii.

Processing of clinical specimens, isolation, identification and antimicrobial susceptibility testing of A. baumannii were done according to standard microbiological procedures. Isolates were classified as Carbapenem Resistant Acinetobacter baumannii (CRAB) and Carbapenem Susceptible Acinetobacter baumannii (CSAB) based on CLSI interpretive criteria.

Clinical data like baseline demographic characteristics, comorbidities, presence of indwelling medical devices, duration of hospital stay including ICU stay, empirical antibiotics given and discharge status of the patient were obtained by reviewing medical records.

Data was analysed using statistical software SPSS Version 25. All the continuous variables were compiled as mean (with standard deviation) or median with interquartile range (IQR) and categorical variables as frequencies (and percentages). The Chi-square test or Fisher's exact test was used to compare categorical variables, while Student's t-test or Mann–Whitney U test was used for comparison of continuous variables. A p value < 0.05 was considered statistically significant.

RESULTS

During the study period, a total of 95 clinically significant isolates of *Acinetobacter baumannii* were included in the analysis. Among these, **50 isolates (52.6%) were resistant** and 45 isolates (47.4%) were susceptible to carbapenems. The majority of isolates were recovered from respiratory specimens, followed by blood, pus, and urine samples. The distribution of these isolates across different specimen types is shown in Figure 1.

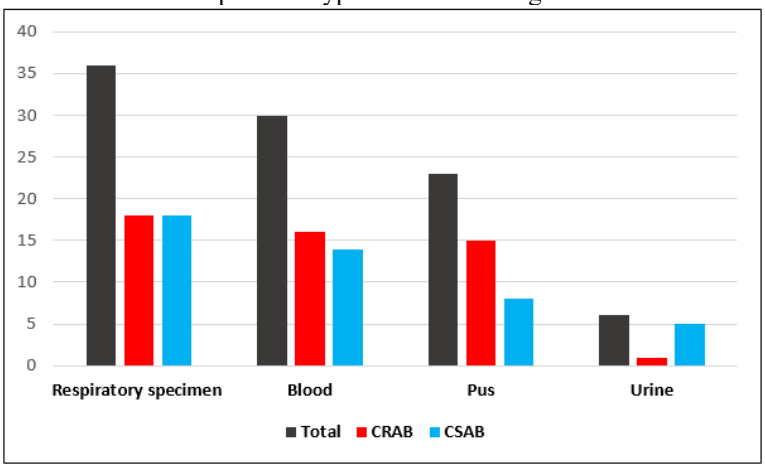

Figure 1 - Distribution of clinical specimens yielding *Acinetobacter baumannii* isolates (n = 95)

Table 1 - Baseline demographic characteristics and comorbidities of patients with CRAB and CSAB infections.

Characteristics	CRAB cases (n=50, %)	CSAB cases (n=45, %)	p value
Age	65.86 ± 10.57	55.3 ± 24.74	0.007
Gender (males)	28 (49.10%)	29 (50.90%)	0.402
Diabetes Mellitus	34 (65.40%)	18 (4.60%)	0.006
Hypertension	36 (67.90%)	17 (32.10%)	0.001
Underlying Respiratory Diseases	17 (70.80%)	7 (29.20%)	0.039
Chronic liver disease	2 (66.70%)	1 (33.30%)	1
Chronic kidney disease	8 (61.50%)	5 (38.50%)	0.489

Various factors including baseline demographics and comorbidities were assessed for patients with *A. baumanii* infections (Table 1). The mean age of patients with CRAB infections were significantly higher than those with infection with carbapenem sensitive strains. Diabetes mellitus, hypertension, and underlying respiratory diseases were also significant predisposing factors in patients with CRAB infections.

The presence of indwelling medical devices was observed among several patients with *Acinetobacter baumannii* infections. However, **these were not significantly associated with infection by carbapenem resistant strains**

Table 2: Association of indwelling medical devices with CRAB and CSAB infections.

Indwelling Device	Category	CRAB n (%)	CSAB n (%)	p value
Mechanical Ventilation	Present	13 (65%)	7 (35%)	0.212
	Absent	37 (49.3%)	38 (50.7%)	
Central Line	Present	4 (50%)	4 (50%)	1.000
	Absent	46 (52.9%)	41 (47.1%)	
Urinary Catheter	Present	2 (28.6%)	5 (71.4%)	0.250
	Absent	48 (54.5%)	40 (45.5%)	

Clinical outcomes of patients with infections with carbapenem resistance and sensitive strains were also compared (**Table 3)**. Empirical antibiotic therapy was not appropriate in most of the patients with CRAB infections. Duration of ICU and hospital stay were significantly longer when compared to those with infections with carbapenem sensitive strains. **Mortality rates were also significantly higher among patients with CRAB infections** (64%) when compared to infections with carbapenem sensitive strains (40%).

Table 3: Clinical outcomes of patients with CRAB and CSAB infections

Characteristics	CRAB cases (n=50)	CSAB cases (n=45)	p value
Appropriate empirical antibiotic therapy	3 (6%)	15 (33.3%)	0.001
ICU stay	3 days (IQR: 10)	0 days (IQR: 3)	0.001
Total Duration of hospital stay	11 days (IQR: 10)	6 days (IQR: 6)	0.001
Mortality	32 (64%)	18 (40%)	0.001

DISCUSSION

Acinetobacter baumannii is an opportunistic pathogen associated with various types of healthcare associated infection (HAIs) particularly in critically ill patients[2]. Unlike gram negative enteric bacteria, *A. baumanii* has the ability to survive for long periods on dry surfaces and nutrient limiting conditions[1]. Treating infections caused by this organism is a therapeutic challenge, as most of these isolates are resistant to carbapenems, which is the most commonly used last line reserve antibiotic against gram negative bacterial infections[8]. The environmental adaptablility of this organism along with its multidrug resistant characteristics, makes the control of nosocomial infections quite challenging, especially in intensive care units.

In the present study, 52.6% of the isolates were resistant to carbapenems. *Resistance in A. baumanii* is mainly due to plasmid borne carbapenemase genes, especially $bla_{\text{OXA-23}}$. These genes are mainly disseminated via horizontal gene transfer, which is responsible for the growing burden of antimicrobial resistance especially in hospital settings[4].

In our study, patients with CRAB infections were significantly older than those with CSAB infections. Advancing age is often associated with higher burden of comorbidities and underlying organ dysfunctions. Among the comorbidities evaluated in our study, diabetes mellitus and hypertension were significantly associated with CRAB infections. The risk of these conditions also increases as one ages, resulting in them to be at increased exposure to hospital environment and prolonged hospitalization. Age related decline in immune function, diabetes associated neutrophilic dysfunction and increased exposure to these multidrug resistant nosocomial pathogens collectively predispose these patients to infections caused by multidrug resistant organisms like CRAB[9,10].

In the present study, underlying respiratory disease was significantly associated with infection by CRAB. This may be related to the fact that *A. baumanii* was mainly isolated from respiratory specimens. *This organism is quite sturdy and can survive* for prolonged periods on hospital surfaces and colonize equipments. Being exposed to variety of antibiotics in the hospital setting, it develops resistance to these drugs[3]. Individuals with chronic respiratory diseases have impaired mucociliary clearance, which facilitates colonization and subsequent infection by opportunistic pathogens[11]. In addition, when in respiratory distress they may often require invasive respiratory support. *Acinetobacter baumannii* is a well-recognized pathogen in ventilator-associated pneumonia and other hospital-acquired respiratory infections. Almost 70% of nosocomial outbreaks due to *A. baumanii* is attributed to ventilator components like ventilator circuits and resuscitation bags[12]. In our study, 20 patients were on ventilators, of which CRAB was isolated in 65% (13/20). In contrast, we did not find any **significant association of CRAB with chronic liver or kidney disease.** This may be due to the relatively smaller number of patients with these conditions in our study and

also the difference in their pattern of healthcare exposure.

Ability of *A. baumannii* to form biofilms on indwelling medical devices is well recognized. Biofilm formation helps the organism to persist in various medical surfaces in hospitals and also provides a protective shield from the effect of antibiotics[13]. We studied the association of CRAB infection in patients with invasive devices like central lines, urinary catheters and ET tubes. However, no statistically significant association was established, suggesting that presence of these devices may increase the risk of infection in these patients, but it may not necessarily predict infection by carbapenem resistant strains

In our study, in 94% of patients with CRAB infections, appropriate antibiotic therapy was initiated only after culture and antibiotic sensitivity reports were available. This delay in start of definitive therapy may result in worsening clinical status of patients as well as increased risk of complications, resulting in significant longer ICU stay[14]. In addition, the longer treatment course often required for these definitive therapeutic agents[15], may also have contributed to the overall extended duration of hospitalization, as observed in this study.

Colistin, the last resort drug against infections with CRAB[6] are considered as Reserve drugs in WHOs Aware classification of antibiotics[16]. To prevent overuse and misuse of these agents in our hospital, 'Form for use of reserve antibiotics' need to be mandatorily filled stating the reason for initiating these drugs as empiric therapy. Hence colistin is often initiated only after antibiotic susceptibility report is available, and this delay in initiation of effective antibiotic may result in poorer outcome in patients with CRAB infections. In our study, mortality rates were significantly higher among patients with CRAB infections (64%) as compared to 44% in patients with infection due to carbapenem sensitive strain. These rates are much higher than those reported in several other studies across the globe (20-40%)[4]. This high variation in mortality rates among CRAB infections could be due to the difference in patient population and health care setting in these studies. Rapid diagnostic methods for identification of organisms along with rapid phenotypic or genotypic resistance determinants can help in earlier detection of resistant organisms and prompt initiation of appropriate antibiotics[16]. On the other hand, formulary restrictions on carbapenems are comparatively lenient, as they belong to Watch group[17], and as their spectrum of activity is much broader[18], they are more commonly used as empiric therapy in severe hospital-acquired infections. Strict adherence to antibiotic policies, judicious use of broad-spectrum antibiotics and timely de-escalation to narrow spectrum antibiotics based on culture results are essential to limit the emergence of multidrug resistant organisms such as CRAB[19].

CONCLUSION

This study highlights the challenges associated with infections by CRAB. Early identification of resistant pathogens, judicious use of antibiotics along with reduction of environmental bioburden by strict implementation of infection prevention and control practices are essential to contain the spread and cross transmission of these resistant organisms. Strengthening all arms of antimicrobial stewardship programme is therefore necessary to limit the emergence and spread of multidrug resistant organisms such as CRAB.

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