Antimicrobial resistance of acinetobacter baumannii infection of lower respiratory tract and mortality – A cross-sectional study from a tertiary care teaching hospital in Kerala

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Abstract

Background: Acinetobacter baumannii has evolved as a common Multi Drug Resistant (MDR) microbe. This study was conducted to find the profile of antimicrobial resistance and mortality and their associated factors in A. baumannii infection of lower respiratory tract.

Materials and Methods: This was a record based cross sectional study done in a tertiary care teaching hospital in Kerala. Records of all the 63, A. baumannii lower respiratory infection in 2017, were retrieved and analyzed. MDR was defined as resistance to at least one agent of three or more antimicrobial classes. Proportion of MDR, carbapenam resistance and resistance to other major antimicrobials were calculated. Determinants of carbapenam resistance and its associated antimicrobial resistance were explored. Proportion of mortality and the associated factors were explored. Student's t-test, chi-square test or fisher exact test were used appropriately.

Results: Proportions of MDR and carbapenam resistance were 85.7% and 41.3% respectively. Highest proportion (90.5%) was resistant to piperazillin-tazobactam. Carbapenam resistance was associated with MDR (p-value<0.05). Mean duration of mechanical ventilation and intensive care unit (ICU) stay prior and after the infection were longer for patients with carbapenam resistant strains (p-value<0.05). Mortality rate was 74.6% (95% CI: 63.9% to 85.3%). Older age and ICU stay prior to infection were associated with mortality (p-value<0.05).

Conclusions: Rates of antimicrobial resistance in Acinetobacter baumannii and the mortality were high in the setting, comparable to reports from other parts of India. The drug resistance increases hospital care burden. There is an urgent need to implement stringent infection control measures.

Keywords: Acinetobacter baumannii; Nosocomial infection; Antimicrobial resistance; Multi Drug Resistance; ESKAPE.

Introduction

The most common and serious Multi Drug Resistance (MDR) pathogens have been encompassed within the acronym "ESKAPE," standing for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species[1]. Acinetobacter baumannii which has become part of ESKAPE was known to be pan-sensitive in 1970's[2]. This microbe has earned a moniker "Iraqibacter" recently because of the concerns it raised in the conflict zones in Iraq[3].

Acinetobacter baumannii is a gram-negative, aerobic, pleomorphic, non-motile coccobacillus of low pathogenecity but has become a serious hospital acquired infection worldwide[4]. The organism has diverse mechanisms for antimicrobial resistance and has acquired resistance to almost all commercially-available antibiotics posing significant challenge to the clinician[4]. Another challenging aspect of the microbe is in distinguishing between colonization and true infection, particularly since many infections occur in the setting of colonization[5].

Data regarding the prognosis of patients with Acinetobacter baumannii infections are limited. This opportunistic pathogen infects immunocompromised individuals, particularly those who have prolonged hospital stay [6]. It was known to be associated with aquatic environments[7]. It colonizes the skin and heavy growth in culture is obtained from the respiratory and oropharyngeal secretions of infected individuals[8]. In recent years, it has been designated as a "red alert" human pathogen due to its extensive antibiotic resistance[9]. Multidrug-resistant (MDR) pathogens have become a cause for serious concern in both nosocomial and community-acquired infections[10]. World Health Organization (WHO) has recently identified antimicrobial resistance as a major threat to public health[11]. In this study, we estimated rates of antimicrobial resistance in Acinetobacter baumannii infection of lower respiratory samples, mortality among the patients affected and associated factors.

Materials and Methods

This was a hospital record based cross sectional study in a tertiary care teaching hospital in south Kerala. The patients were identified from the microbial culture records register, maintained by the department of microbiology. Medical records were retrieved of all the patients whose lower respiratory tract samples, such as bronchoalveolar lavage, mini bronchoalveolar lavage or sputum turned culture positive for Acinetobacter baumannii. The sample size was 63, calculated for an expected prevalence of 88% for MDR, with precision of 8% and α error of 5%[12]. The sample size was achieved by exhaustive sampling over the year 2017.All the positive cultures were tested for antimicrobial

susceptibility to ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, piperacillin-tazobactam, imipenem, and meropenem. Strains with intermediate susceptibility were considered resistant.

The data collected from medical records were on the antimicrobial resistance, age, gender, hospital setting where the samples were referred, and length of mechanical ventilation before and after Acinetobacter baumannii infection, length of hospital stay and ICU stay after infection, antimicrobial agents administered during hospitalization before Acinetobacter baumannii infection and cause of death. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as frequency and percentages. Student's t-test, chi square test or fisher exact test were used appropriately in analysis.

Definitions

Nosocomial lower respiratory infection: At least two of the respiratory signs or symptoms which appear 48 hours after hospitalization among the following – cough, purulent sputum, new infiltrate on chest radiograph consistent with infection[13].

Definitions for the Acinetobacter baumanni antimicrobial resistance used in the study were as follows.

Carbapenem-resistance: Resistance to both imipenem and meropenem

Carbapenem-sensitive: Sensitive to imipenem or meropenem.

Multi Drug Resistance: Resistance to at least one agent of three or more antimicrobial classes [14].

Results

During the year 2017, total of 63 Acinetobacter baumannii respiratory isolates were obtained in the microbiology department from the hospital. All of them were nosocomial infections. Thirty two cultures showed polymicrobial infections. Most common organism isolated in lower respiratory specimens along with Acinetobacter baumanni infection was ESBL positive Klebsiella pneumoniae. Mean age of the patients was 65.5 years (SD=14.1). The proportion of older persons (age 65 years and above) was 69.8% (n=44).There were 41 (65.1%) males and 22 (34.9%) females. Majority of infections (57, 90.5%) occurred in patients admitted in Intensive Care Units who were also on mechanical ventilation.

The pattern of drug resistance of the Acinetobacter baumannii isolates is depicted in figure 1. Proportion of carbapenam resistant isolates was (n=26) 41.3%. Proportion of multi drug resistance (MDR) was (n=54) 85.7% (95% CI: 77.1% to 94.3%). The resistance was highest (60, 95.2%) for piperazillin-tazobactum. Carbapenam susceptibility was significantly associated with susceptibility to ceftazidime, cefepime, gentamicin (p-value < 0.05) (Table 1). Carbapenam resistance was significant indicator of multi drug resistance (p-value < 0.05) (Table 1). Among the carbapenam resistant strains all were MDR, resistant to piperazillin-tazobactam and resistant to ceftazidime; 96% were resistant to ciprofloxacin and gentamicin; 85% were resistant to amikacin.

Factors affecting carbapenam susceptibility were analyzed and depicted in Table 2. Mean duration of stay in Intensive Care Unit (ICU) and mean duration of mechanical ventilation prior to the infection were significantly longer among those who had carbapenam resistant strains. Duration of hospital stay was not associated with carbapenam susceptibility. Prior use of carbapenam was not a risk factor for resistance. The patients, who had carbapenam resistant strains thereafter, had significantly longer duration of hospital stay, ICU stay and mechanical ventilation (Table 3).

Mortality rate among Acinetobacter baumannii infected patients was 74.6% (95% CI: 63.9% to 85.3%) (n=47). Factors associated with mortality were older age (65 years and above) and ICU stay before infection (p-value<0.05). Multi drug resistance and carbapenam resistance were not associated with mortality (Table 4).

Discussion

The strength of the study is that the data is from a quality controlled tertiary care microbiology laboratory. The major limitation is that the results may not be generalized since the study was conducted in single center. The study was focused on nosocomial lower respiratory infections due to Acinetobacter baumannii. Among the nosocomial infections, pneumonia is the most common and the organisms are most commonly are gram negative, particularly Acinetobacter baumannii in ICUs[15]. All the Acinetobacter baumannii infections were nosocomial. It has uncanny ability to survive for prolonged periods in hospital environment[16-18]. The organism commonly targets the most vulnerable hospitalized patients, those who are critically ill with breaches in skin integrity and airway protection[15]. In our study, it was seen that 90% of infections occurred among the patients in ICUs, who were also on mechanical ventilation.

Acinetobacter baumannii are intrinsically resistant to many antibiotics attributed to a slow porin channel mechanism in it[19]. Resistance of Acinetobacter baumannii to carbapenems and antibiotics of other classes varies depending on the country and hospital, but a trend towards increasing resistance to carbapenems is being observed[20,21]. Exposure to broad-spectrum antibiotics, such as carbapenems, has been identified as a risk factor for acquisition of imipenem-resistant Acinetobacter in studies[9,20]. Studies have shown that the prior use of carbapenems, third-generation cephalosporins, and/or fluoroquinolonesare risk factor for the acquisition of MDR Acinetobacter baumannii[9,18]. In our study, carabapenam resistance was seen in 41% of the isolates and all of them were multi drug resistant as well. Prior

use of carbapenams was not associated with carbapenam resistance in this study but, the sample size was not powered to find the association. Studies have demonstrated that carbapenem resistant strains can become resistant to all antibiotics[20,22]. Proportion of multi drug resistance was 85.7% (95% CI: 77.1% to 94.3%) which is comparable to reports from Varanasi in North India (88%) and Nashik in western India (89.4% to 95.9% over four years)[12,23]. The highest proportion of resistance was to piperacillin-tazobactam (95%) in this study. In a study from Nashik, the proportions of resistant strains to most of the antibiotics were above 77.5%[23]. Longer duration of ICU stay and mechanical ventilation were seen to be factors associated with acquisition of carbapenam resistant strains in our study. This calls for more stringent infection control action plan in the ICUs[11].

The mortality among Acinetobacter baumannii infected patients was 74.6% (95% CI: 63.9% to 85.3%) in this study. This result is comparable to a study reported from a centre in North India[24]. A study from Korea had reported 30 day mortality rate of 34% which would be regarded as quite low[25]. The differences may be attributed to the ICU facilities and patient profile. Older age and ICU stay were associated with mortality in our study. MDR and carbapenam resistance were not associated with mortality but, the sample size was not powered to find these associations. Many other risk factors for mortality were not studied and multivariate analysis could not be done to adjust for the confounders due to sample size constraints. There are studies which reported higher mortality due to carbapenam resistant strains[26,27], but many other studies did not find such an association[27-31]. Antimicrobial resistance leads to higher health care expenditure [11]. This was reflected in our study as the acquisition of carbapenam resistant strains was associated with longer duration of mechanical ventilation, ICU stay and hospital stay.

Table 1: Association of carbapenam susceptibility with susceptibility to other antimicrobials, of Acinetobacter baumannii (N=63)

Susceptibility to other antimicrobials		Carbapenam susceptibility		p -Value
		Resistant (n=26)	Sensitive (n=37)	
		n (%)	n (%)	
Piperacillin-tazobactam	Resistant	26 (100%)	34 (91.9%)	0.261
	Sensitive	0 (0%)	3 (8.1%)	
Ceftazidime	Resistant	26 (100%)	30 (81.1%)	0.035
	Sensitive	0 (0%)	7 (18.9%)	
Cefepime	Resistant	17 (65.4%)	14 (37.8%)	0.031
	Sensitive	9 (34.6%)	23 (62.2%)	
Ciprofloxacin	Resistant	25 (96.2%)	29 (78.4%)	0.105
	Sensitive	1 (3.8%)	8 (21.6%)	
Gentamicin	Resistant	25 (96.2%)	27 (73.0%)	0.040
	Sensitive	1 (3.8%)	10 (27.0%)	
Amikacin	Resistant	22 (84.6%)	28 (75.7%)	0.584
	Sensitive	4 (15.4%)	9 (24.3%)	
Ampicillin-sulbactam	Resistant	11 (42.3%)	17 (45.9%)	0.775
	Sensitive	15 (57.7%)	20 (54.1%)	
Multi Drug Resistance	Yes	26 (100%)	28 (75.7%)	0.008
	No	0 (0%)	9 (24.3%)	
Note: Proportions are depicted column-wise				

Table 2: Risk factors for acquiring carbapenem-resistant Acinetobacter baumannii infection (N=63)

Plausible risk factors		Carbapenam susceptibility		p -Value
		Resistant (n=26)	Sensitive (n=37)	
Duration of hospital stay prior to infection (days) (Mean, SD)		13.59, 8.05	10.35, 8.19	0.125
Duration of ICU stay prior to infection (days) (Mean, SD)		7.92, 6.74	4.17, 3.61	0.006
Duration of mechanical ventilation before infection (days) (Mean, SD)		7.07, 5.79	3.25, 2.61	<0.001
Prior carbapenem use (n, %)	Present	4, 80.0%	1, 20.0%	0.150
	Absent	22, 37.9%	36, 62.1%)	

SD - standard deviation
Note: Proportions are depicted raw-wise

Table 3: Association of carbapenam resistance of Acinetobacter baumannii with hospital care burden (N=63)

Hospital care burden in terms of duration	Carbapenam susceptiblity		p -value
	Resistant (n=26)	Sensitive (n=37)	
	Mean, SD	Mean, SD	
Duration of hospital stay after infection (days)	35.63, 27.44	22.89, 14.76	0.020
Duration of ICU stay after infection (days)	36.12, 27.52	19.33, 14.51	0.003
Duration of mechanical ventilation after infection (days)	11.31, 7.34	5.37, 5.03	0.001

SD – standard deviation, ICU – Intensive Care Unit

Table 4: Factors associated with in-hospital mortality among Acinetobacter baumannii infected patients (N=63)

Risk factors and categories		Died in-hospital (n = 47)	Survived (n = 16)	p -Value
Age in years	≥ 65	38 (86.4%)	6 (13.6%)	0.001
	< 65	9 (47.4%)	10 (52.6%)	
ICU stay before infection	Present	45 (78.9%)	12 (21.1%)	0.032
	Absent	2 (33.3%)	4 (66.7%)	
Resistance to carbapenems	Present	23 (88.5%)	3 (11.5%)	0.068
	Absent	24 (64.9%)	13 (35.1%)	
Multi Drug Resistance	Present	43 (79.6%)	11 (20.4%)	0.067
	Absent	4 (44.4%)	5 (55.6%)	
ICU – Intensive Care Unit Proportions are depicted raw-wise				

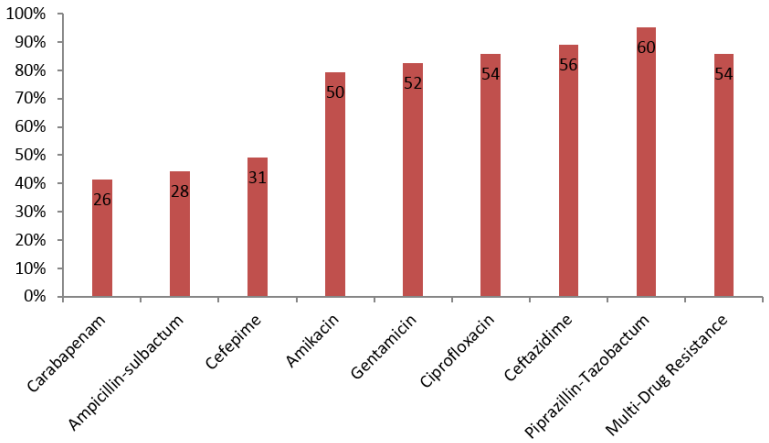

Fig. 1: Antimicrobial resistance pattern in the Acinetobacter baumannii isolates (N=63)

Conclusion

Anti-microbial resistance of Acintobacter baumannii and mortality among the infected patients is high in this tertiary care teaching hospital in Kerala and is comparable to similar study settings in other parts of India. Carbapenam resistance is associated with multi drug resistance. Longer duration of ICU stay and longer duration of mechanical ventilation can lead to acquisition of resistant strains. Resistant strains lead to increased hospital care burden. In the light of the current study, stringent infection control measures are recommended.

Conflicts of interest: None declared
Acknowledgements: None

References

1. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* 2008;197:1079–81
2. Fournier PE, Vallenet D, Barbe V, Audic S, Ogata H, Poirel L, et al. Comparative genomics of multidrug resistance in Acinetobacterbaumannii. *PLoS Genet* 2006;2:e7
3. CDC Acinetobacter baumannii infections among patients at military medical facilities treating injured U.S. service members, 2002-2004. *JAMA* 2004; 292:2964–6

4. Fournier PE, Richet H. The epidemiology and control of Acinetobacter baumannii in health care facilities. *Clin Infect Dis* 2006; 42:692.
5. Albrecht MC, Griffith ME, Murray CK, et al. Impact of Acinetobacter infection on the mortality of burn patients. *J Am Coll Surg* 2006; 203:546.
6. Montefour K, Frieden J, Hurst S, Helmich C, Headley D, Martin M, et al. Acinetobacter baumannii: an emerging multidrug-resistant pathogen in critical care. *Crit Care Nurse* 2008;28:15–25
7. Turton JF, Kaufmann ME, Gill MJ, Pike R, Scott PT, Fishbain J, et al. Comparison of Acinetobacter baumannii isolates from the United Kingdom and the United States that were associated with repatriated casualties of the Iraq conflict. *J Clin Microbiol* 2006;44:2630–4.
8. Sebeny PJ, Riddle MS, Petersen K. Acinetobacterbaumannii skin and soft-tissue infection associated with war trauma. *Clin Infect Dis* 2008;47:444–9
9. Cerqueira GM, Peleg AY. Insights into Acinetobacter baumannii pathogenicity. *IUBMB Life* 2011;63:1055–60.
10. Peleg AY, Seifert H, Paterson DL. Acinetobacterbaumannii: emergence of a successful pathogen. *Clin Microbiol Rev* 2008;21:538–82
11. Antimicrobial resistance. WHO. Available from: http://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistanceKey facts [accessed October 2018]
12. Banerji T, Mishra A, Das A, Sharma S, Barman H, Yadav G. High Prevalence and Endemicity of Multidrug Resistant Acinetobacter spp. in Intensive Care Unit of a Tertiary Care Hospital, Varanasi, India. *J Pathol* 2018;2018:9129083.
13. Ducell G, Fabry J, Nicolle L. Prevention of Hospital-Acquired Infections, a Practical Guide. 2nd Ed. Department of Communicable Disease, Surveillance and Response, World Health Organization. Malta; 2002:4.
14. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al . Multidrug-resistant, extensively drug resistant and pan drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance .*Clin Microbiol Infect* 2012;18:268–81.
15. Ghanshani R, Gupta R, Gupta BS, Kalra S, Khedar RS, Sood S. Epidemiological study of prevalence, determinants, and outcomes of infections in medical ICU at a tertiary care hospital in India. *Lung India* 2015;32(5):441-48.
16. Wendt C, Dietze B, Dietz E, Rüden H. Survival of Acinetobacter baumannii on dry surfaces. *J Clin Microbiol* 1997;35:1394.
17. Bernards AT, Harinck HI, Dijkshoorn L, et al. Persistent Acinetobacter baumannii? Look inside your medical equipment. *Infect Control Hosp Epidemiol* 2004; 25:1002.
18. Getchell-White SI, Donowitz LG, Gröschel DH. The inanimate environment of an intensive care unit as a potential source of nosocomial bacteria: evidence for long survival of Acinetobactercalcoaceticus. *Infect Control Hosp Epidemiol* 1989;10:402.
19. Sugawara E, Nikaido H. OmpA is the principal nonspecific slow porin of Acineto bacterbaumannii. *J Bacteriol* 2012;194:4089–96.
20. Baran G, Erbay A, Bodur H, Onguru P, Akinci E, Balaban N, et al . Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. *Int J Infect Dis* 2008;12:16–21.
21. Dent LL, Marshall DR, Pratap S, Hulette RB. Multidrug resistant *Acinetobacterbaumannii*: a descriptive study in a city hospital. *BMC Infect Dis* 2010;10:196.
22. Munoz-Price LS, Zembower T, Penugonda S, Schreckenberger P, Lavin MA, Welbel S, et al. Clinical outcomes of carbapenem-resistant Acinetobacterbaumannii bloodstream infections: study of a 2-state monoclonal outbreak. *Infect Control Hosp Epidemiol* 2010;31:1057–62.
23. Odsbu I, Khedkar S, Khedkar U, Nerkar SS, Tamhankar AJ, Lundborg CS. High Proportions of Multidrug-Resistant *Acinetobacter* spp. Isolates in a District in Western India: A Four-Year Antibiotic Susceptibility Study of Clinical Isolates. *Int J Environ Res Public Health* 2018;15(1):153
24. Mathai AS, Oberoi A, Madhavan S, Kaur P. *Acinetobacter* infections in a tertiary level intensive care unit in northern India: Epidemiology, clinical profiles and outcomes. *J Infection Public Health* 2012;5(2):145-52.
25. Park SY, Choo JW, Kwon SH, Yu SN, Lee EJ. Kim TH, Choo EJ, Jeon MH. Risk Factors for Mortality in Patients with *Acinetobacter baumannii* Bacteremia. *Infect Chemother* 2013;45(3):325–30.
26. Wareham DW, Bean DC, Khanna P, Hennessy EM, Krahe D, Ely A, et al. Blood stream infection due to Acinetobacterspp: epidemiology, risk factors and impact of multidrug resistance. *Eur J Clin Microbiol Infect Dis* 2008;27:607–12.
27. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. *J Hosp Infect* 2007;65:204–11
28. Aydemir H, Celebi G, Piskin N, Oztoprak N, Keskin AS, Aktas E, et al. Mortality attributable to carbapenem-resistant nosocomial Acinetobacterbaumannii infections in a Turkish university hospital. *Jpn J Infect Dis* 2012;65:66–71.
29. Sunenshine RH, Wright MO, Maragakis LL, Harris AD, Song X, Hebden J, et al. Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. *Emerg Infect Dis* 2007;13:97–103.
30. Huang ST, Chiang MC, Kuo SC, Lee YT, Chiang TH, Young SP, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant Acinetobacter baumannii bacteremia . *J Microbiol Immunol Infect* 2012;45:356–62.
31. Routsi C, Pratikaki M, Platsouka E, Sotiropoulou C, Nanas S, Markaki V, et al. Carbapenem-resistant versus carbapenem-susceptible Acinetobacter baumannii bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes. *Infection* 2010;38:173 – 80.

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