ORIGINAL ARTICLE

FREQUENCY AND CLINICAL SPECTRUM OF MULTIDRUG RESISTANT *ACINETOBACTER BAUMANNII* AS A SIGNIFICANT NOSOCOMIAL PATHOGEN IN INTENSIVE CARE UNIT PATIENTS

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Background: *Acinetobacter baumannii* has emerged as one of the leading causes of multidrug resistant nosocomial infections worldwide. It is able to survive in hospital environment and build up diverse resistance mechanisms making it difficult to treat with current antibiotics. **Objective:** It was to determine the frequency and patterns of *Acinetobacter baumannii* in intensive care units (ICU) settings. **Methods:** A cross sectional study was carried out in the Department of Microbiology, Armed Forces Institute of Pathology, Rawalpindi, from 1st July 2017 to 30th June 2019. A total of 603 non-duplicate clinical specimens were received from intensive care units. Specimens yielding growth of multidrug resistant *Acinetobacter baumannii*, were evaluated as per standard protocol. The antimicrobial sensitivity testing was performed as per Clinical and Laboratory Standard Institute guidelines (2017-2018). **Results:** Among *Acinetobacter baumannii* (310 isolates), 5% were multidrug resistant, 93% extensively drug resistant and 1% pan drug resistant. Percentage of carbapenem resistant strains was 92%. In drugs like tigecycline and polymyxin, resistance was noted as 73% and 1% respectively. High yield of this superbug was mainly obtained from respiratory specimens (43.5%), whereas 24% were detected from wound infections and 29% from other samples. **Conclusion:** This study showed a rapidly increasing resistance in *Acinetobacter baumannii*. Therefore, polymyxin remains the only option in our intensive care units, but its usage as empirical therapy in our setting has led to the emergence of resistance to this drug. Implementing infection control practices, antimicrobial stewardship and restricted use of polymyxin can play a significant role in reducing health care burden.

Keywords: Nosocomial infections; Intensive care units; Multidrug resistance; Extensive drug resistance; Pandrug resistance, Carbapenem resistance.

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INTRODUCTION

Acinetobacter baumannii (*A. baumannii*) is an important member of ESKAPE pathogens, accounting for almost 3–6% of all nosocomial infections worldwide.[1] It has ability to survive in the hospital environment for a longer period due to biofilm formation mainly on indwelling catheters, nebulizers, and ventilator devices. In addition to that, it can accumulate multiple resistant genes which makes it notorious for causing catheter related bloodstream infections, urinary infections, or shunt related infections.[2] This opportunistic pathogen, due to its multidrug resistant (MDR), extensively drug resistant (XDR) and carbapenem resistant (CRAb) potential, has become a global challenge in ICU settings.[3,4] WHO has already included this lethal bug in priority 1 critical list for research and development of new antibiotics.[4] The emergence of these resistant strains has led to increased usage of last resort drugs like polymyxin and tigecycline. Injudicious usage, inappropriate dosage, and lack of awareness about antibiotic stewardship protocols have resulted in the rise of pan-drug resistant (PDR) strains.[3,5] Therefore, it is necessary to know the current treatment options and utility of last resort drugs in ICUs for the administration of effective empirical therapy. It is also necessary to differentiate between colonization and infection to avoid unnecessary use of antimicrobials. This will not only reduce the morbidity and mortality rate due to highly resistant hospital acquired infections but also curtail the economic burden.[6]

The purpose of this study was to determine the frequency, changing susceptibility patterns, and possible treatment options for multidrug resistant *A. baumannii* infections in ICUs of a tertiary care hospital and to correlate with the clinical condition of the respective patients.

MATERIAL AND METHODS

A descriptive cross sectional study was conducted at the Department of Microbiology, Armed Forces Institute of Pathology (AFIP), in collaboration with

surgical and medical ICUs of Combined Military Hospital, Rawalpindi from 01st July 2017 to 30th June 2019. Permission was taken from the Institutional Review Board and the Ethical Committee. Informed consent was taken from all patients /attendants included in this study but their identities were kept confidential.

A. baumannii strains isolated from various clinical specimens like non directed bronchial lavage (NBL), broncheoalveolar lavage (BAL), endobronchial washings (EBW), pleural fluid, sputum, tracheal aspirate, blood, urine, cerebrospinal fluid (CSF), central venous catheter (CVP) tip, pus, pus swab and tissue collected from patients admitted in ICUs were included in this study. Clinical details of patients like prior usage of antibiotics, previous hospital admission, and comorbid conditions were noted. Clinical correlation with our lab results were made to differentiate between colonization and infection. "Infection" was defined as patients, with positive cultures with *A. baumannii,* showing clinical signs and symptoms of disease along with lab parameters of infection (Total leucocyte count and platelets count, C-reactive protein CRP and Procalcitonin) and X-ray chest findings for respiratory infections. While "colonization" was defined as positive cultures with *A. baumannii* in the absence of specific clinical findings.

All specimens were processed as per standard microbiological procedures. The isolates were identified based on colony morphology, basic biochemical tests, API 20NE (Biomerieux, France), and VITEK-2 system (Biomerieux, France). Antimicrobial susceptibility testing (AST) was done by a modified Kirby-Bauer disk diffusion method on Mueller Hinton agar (Oxoid, UK). Antimicrobial susceptibility was also confirmed by VITEK-2 system (Biomerieux, France). The antibiotic discs (Oxoid, UK) of different concentrations were applied according to Clinical and Laboratory Standard Institute (CLSI 2017-2018) guidelines including amikacin 30 µg, ceftazidime 30 µg, ciprofloxacin 5 µg, gentamicin 10 µg, ceftriaxone 30µg, trimethoprim-sulfamethoxazole 25 µg, cefepime 30 µg, imipenem 10 µg, meropenem 10 µg, piperacillin-tazobactam 110 µg, minocycline 30µg, doxycycline 30µg, ampicillin-sulbactam 105µg, and tobramycin 10 µg.[7] For colistin, susceptibility testing was done by the broth microdilution method. For tigecycline, the breaking point by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) against Enterobacteriaceae were followed.[8,9] Based on susceptibility the isolates were classified as MDR (resistant to at least one drug in 3 or more classes of antibiotics), XDR (resistant to at least one drug in all but 2 or less antimicrobial classes), PDR (resistant to all drugs in all classes of antibiotics) and CRAb (resistant to either imipenem or meropenem or both drugs).[3] For Quality control testing, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, and *A. baumannii* ATCC BAA 747 (American Type Culture Collection, Rockville, MD) were used as controls. Data was analysed using SPSS (version 24).

RESULTS

A total of 310 non-duplicate different clinical specimens yielding growth of *A.baumannii* were analyzed during the chosen study period. The mean age at admission was 42±20.5 years. 69% (214) of total patients were males and 31% (96) were females.

The highest yield was detected in respiratory samples. It accounted for 43% (133) of the total. All these patients were either on ventilator support/ tracheal intubation or using humidifiers. Ventilator associated pneumonia (VAP) accounted for 35% (45) of total nosocomial infections (127) followed by central line associated blood stream infections (CLABSI) 19.6% (25). The mortality rate noted in VAP patients with Carbapenem-resistant *A.baumannii* (CRAb) was 10% (31). The second largest yield was detected in samples from wound infections of surgical sites, burns, and bedsores. It accounted for 24%. (Table-1).

Antimicrobial susceptibility pattern was determined by using 16 antibiotics drug panel as per CLSI guidelines (2017-2018) shown in Figure-1. Among *A.baumannii* strains, 5% (17) were MDR, 93% (288) were XDR and 1% (4) were PDR. CRAb isolates accounted for 92% (286). This showed an increase in CRAb strains with the emergence of PDR strains causing prolonged hospital stay, delayed cure, and economic burden. 24% isolates were found resistant to minocycline, 41% to doxycycline, and 1% to colistin. Colistin and minocycline thus showed better sensitivity as compared to all other drugs.

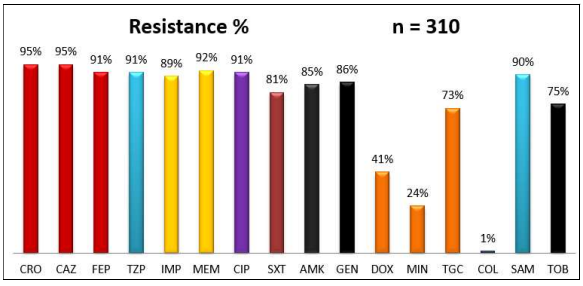

Figure-1: Antimicrobial susceptibility pattern of *Acinetobacter baumannii* strains isolated from ICU patient's specimens

Key: Ceftriaxone (CRO), Ceftazidime (CAZ), Cefipime (FEP), Piperacillin-Tazobactam (TZP), Imipenem (IMP), Meropenem (MEM), Ciprofloxacin (CIP), Trimethoprim-sulfamethoxazole (SXT), Amikacin (AMK), Gentamicin (GEN), Doxycycline (DOX), Minocycline (MIN), Tigecycline (TGC), Colistin (COL), Ampicillin-sulbactam (SAM), Tobramycin (TOB)

Table-1: Distribution of MDR *Acinetobacter baumannii* strains isolated from various clinical specimens and clinical details of patients

		Total *A. baumannii* isolated from Surgical & Medical ICUs (n = 310)				
Gender& Age group	**Comorbid & Risk factors**	**Respiratory specimens: 133 (43%)**	**Wound Specimens: 74 (24%)**	**Others: 103 (33%)**	**Suspected Nosocomial Infections 127 (41%)**	**Multidrug Resistance %age**
Male: 214 (69%)	Diabetics:121 (39%)	[1]NBL: 79 (59%)	Pus: 34 (46%)	Blood: 46(45%)	[2]VAP:45 (35%)	MDR: 17(5%)
Female: 96 (31%)	Heart diseases: 108 (35%)	[1]BAL: 25 (19%)	Pus Swab: 25 (34%)	CSF: 07 (7%)	[2]CLBSI: 25 (19.6%)	XDR: 288(93%)
12-40 years: 105 (34%)	Chronic Kidney diseases: 81(26%) More than one Comorbids: 211(68%)	Tracheal Secretions: 09 (7%)	Tissue: 15 (20%)	Pleural Fluid: 10 (10%)	[2]SSI: 15(11.8%)	PDR: 4 (1%)
>40years: 205 (66%)	Multiple hospital admissions: 130(42%)	Sputum: 08 (6%)		Urine: 13 (13%)	[2]CAUTI: 7(5.5%)	CRAb: 286 (92%)
Mortality: 31(10%)	Prior Antibiotics usage: 280(90%) More than one lines in place: 227 (73%)	[1]EB Washings: 12(9%)		CVP Tip: 27(26%)	[2]CSFshunt infections: 5 (4%)	
	Infection Vs Colonization : Infected: 127(41%) Colonized: 183(59%)				Bacteremia: 30 (23.6%)	

[1]NBL: Non directed bronchial lavage, BAL: Broncheoalveolar lavage, EB: Endobronchial washings
[2]VAP: Ventilator associated pneumonia, CLBSI: Central line associated blood stream infections, SSI: Surgical site infections, CAUTI: Catheter associated urinary tract infections, CSF: Cerebrospinal fluid

DISCUSSION

A. baumannii is notorious for causing lethal infections in hospital settings because of its resistant nature and ability to evade host immunity by virulence factors. It has become a major threat these days due to progressive multi-drug resistance responsible for poor clinical outcomes. It grows well in humid atmosphere, so it easily colonizes the skin, respiratory tract, gastrointestinal tract, and oral cavity. These unique features make it capable of causing hospital outbreaks and a wide range of diseases from wound infections to nosocomial pneumonia, sepsis, and meningitis.[10]

Serious efforts are required to curtail the infection rate by minimizing its environmental colonization with a strict infection control policy.[11] The present study revealed the highest yield of *A.baumannii* from respiratory specimens (43.5%) followed by pus and blood cultures, showing similar results to other studies.[12,13] The incidence rates of ventilator associated pneumonia (VAP), surgical site infection (SSI), central line-associated bloodstream infections (CLBSI), catheter-associated urinary tract infection (CAUTI) and shunt related infections were comparable to the rates mentioned by Kanafani Z.[11] Though there is geographic variation in antibiotic resistance, all the studies demonstrated an increasing trend in resistance mainly to third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems.[14,15] Carbapenems were used extensively as the empirical and sole therapy for treating MDR infections in most of the ICUs. This over-usage resulted in the rise of CRAb isolates in our setup as well.[15,16] The present study showed resistance to all primary drugs used, with better susceptibility recorded for minocycline, doxycycline, and colistin. Tigecycline was found resistant in 73% of cases. Our results showed disagreement with a similar study done in India.[17] Another study

showed higher colistin resistance (6.6%) whereas lower tigecycline and minocycline resistance rates compared to our results.[18] The risk factors associated with the prevalence of MDR, XDR, and PDR isolates are prolonged ICU stays unnecessary usage of broad spectrum antibiotics and devices which were also associated with these infections in our cases.[19] Presence of co-morbid conditions like diabetes, chronic obstructive diseases, or renal failure can further deteriorate the clinical effect.[20] The mortality rate among CRAB strains varies from 10–43% especially in VAP patients which was similar to our findings (10%).[21] Tigecycline and colistin are now being used as last resort drugs so their results need to be reported cautiously as both have susceptibility testing issues.[22] Though polymyxin is a nephrotoxic drug but in a low dose in combination with tigecycline it can give favorable results.[23] Nonetheless, there is limited clinical data favoring combination therapy over monotherapy in reducing the mortality rate.[24] Colistin alone has a better prognosis but requires careful dosage and knowledge of its pharmacokinetics.[25,26] These XDR strains prevail in hospital settings due to lack of a multifaceted approach thus resulting in unnecessary burden on the hospital. Similar key factors are observed in Wenzler E *et al* study responsible for persistent infections such as over usage of carbapenems in patients and poor infection control practices.[26]

CONCLUSION

This study indicates a daunting situation with rising resistance trends among *A. baumannii* strains and the emergence of PDR *A. baumannii* strains that are not only difficult to eradicate but also increase mortality and morbidity among ICU patients. To combat this, we need to strictly adhere to infection control measures and environmental decontamination to prevent its colonization. Early diagnosis, antibiogram-optimized treatment regimens to save polymyxin, and extensive antimicrobial stewardship programs are required. Continuous surveillance with risk assessment and outbreak recognition can help in curtailing the mortality and spread of infection.

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Informed consent: Informed consent was taken from all patients/attendants.

AUTHORS' CONTRIBUTION

FS,AH: Conceptualization, literature search, Data collection, analysis and interpretation, write up. WH, GZ, WA, AI, LS: Study design, Data analysis, interpretation, proof reading.

REFERENCES

1. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, *et al*. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol 2016;37(11):1288–301.
2. Greene C, Vadlamudi G, Newton D, Foxman B, Xi C. The influence of biofilm formation and multidrug resistance on environmental survival of clinical and environmental isolates of Acinetobacter baumannii. Am J Infect Control 2016;44(5):e65–71.
3. Kanafani Z, Kanj S. Acinetobacter infection: Treatment and prevention options. Wolters Kluwer 2013;2:20–5.
4. Shrivastava SR, Shrivastava PS, Ramasamy J. World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. J Med Soc 2018;32(1):76.
5. Fowler LH, Lee S. Antibiotic trends amid multidrug-resistant gram-negative infections in intensive care units. Crit Care Nurs Clin North Am 2017;29(1):111–8.
6. Asim P, Naik NA, Muralidhar V, Vandana KE, Varsha AP. Clinical and economic outcomes of *Acinetobacter*vis a vis non-*Acinetobacter* infections in an Indian teaching hospital. Perspect Clin Res 2016;7(1):28–31.
7. Patel JB, Weinstein M, Eliopoulos G, Jenkins S, Lewis J, Limbago B. M100 Performance standards for antimicrobial susceptibility testing. United State: Clinical and Laboratory Standards Institute; 2017.
8. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. [Internet]. Version 7.1, 2017 [cited 2020 Aug]. Available from: http://www.eucast.org
9. Clinical Laboratory Standards Institute. M100: performance standards for antimicrobial susceptibility testing: 28th informational supplement; 2018.
10. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and pathophysiological overview of Acinetobacter infections: a century of challenges. Clin Microbiol Rev 2017;30(1):409–47.
11. Kanafani Z, Kanj S. Acinetobacter infection: Epidemiology, microbiology, pathogenesis, clinical features, and diagnosis. Wolters Kluwer 2013;2:21–33.
12. Lynch JP, Zhanel GG, Clark NM. Infections due to Acinetobacter baumannii in the ICU: treatment options. Semin Respir Crit Care Med 2017;38(3):311–25.
13. Sohail M, Rashid A, Aslam B, Waseem M, Shahid M, Akram M, *et al*. Antimicrobial susceptibility of Acinetobacter clinical isolates and emerging antibiogram trends for nosocomial infection management. Rev Soc Bras Med Trop 2016;49(3):300–4.
14. Zilberberg MD, Kollef MH, Shorr AF. Secular trends in Acinetobacter baumannii resistance in respiratory and blood stream specimenss in the United States, 2003 to 2012: A survey study. J Hosp Med 2016;11(1):21–6.
15. Neves FC, Clemente WT, Lincopan N, Paião ID, Neves PR, Romanelli RM, *et al*. Clinical and microbiological characteristics of OXA-23-and OXA-143-producing Acinetobacter baumannii in ICU patients at a teaching hospital, Brazil. Brazilian J Infect Dis 2016;20(6):556–63.
16. Nageeb W, Metwally L, Kamel M, Zakaria S. In vitro antimicrobial synergy studies of carbapenem-resistant

Acinetobacter baumannii isolated from intensive care units of a tertiary care hospital in Egypt. J Infect Public Health 2015;8(6):593–602.
17. Sarada V, Rao R, Mani R, Ramana KV. "Colistin, Polymyxin B and Tigecycline Suspectibility to MetalloBetalactamase Producing *Acinetobacter Baumannii* Isolated From Tertiary Health Care Hospital." Am J Microbiol Res 2014;2(2):60–2.
18. Park GE, Kang CI, Cha MK, Cho SY, Seok H, Lee JH, *et al*. Bloodstream infections caused by Acinetobacter species with reduced susceptibility to tigecycline: clinical features and risk factors. Int J Infect Dis 2017;62:26–31.
19. Guo N, Xue W, Tang D, Ding J, Zhao B. Risk factors and outcomes of hospitalized patients with blood infections caused by multidrug-resistant Acinetobacter baumannii complex in a hospital of Northern China. Am J Infect Control 2016;44(4):e37–9.
20. Brotfain E, Borer A, Koyfman L, Saidel-Odes L, Frenkel A, Gruenbaum SE, *et al*. Multidrug resistance acinetobacter bacteremia secondary to ventilator-associated pneumonia: risk factors and outcome. J Intensive Care Med 2017;32(9):528–34.
21. Özvatan T, Akalın H, Sınırtaş M, Ocakoğlu G, Yılmaz E, Heper Y, *et al*. Nosocomial Acinetobacter pneumonia: Treatment and prognostic factors in 356 cases. Respirology 2016;21(2):363–9.
22. Piewngam P, Kiratisin P. Comparative assessment of antimicrobial susceptibility testing for tigecycline and colistin against Acinetobacter baumannii clinical isolates, including multidrug-resistant isolates. Int J Antimicrob Agents 2014;44(5):396–401.
23. Lee CR, Lee JH, Park M, Park KS, Bae IK, Kim YB, *et al*. Biology of Acinetobacter baumannii: pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017;7:55.
24. López-Cortés LE, Cisneros JM, Fernández-Cuenca F, Bou G, Tomas M, Garnacho-Montero J, *et al*. Monotherapy versus combination therapy for sepsis due to multidrug-resistant Acinetobacter baumannii: analysis of a multicentre prospective cohort. J Antimicrob Chemother 2014;69(11):3119–26.
25. Lin MF, Lan CY. Antimicrobial resistance in Acinetobacter baumannii: From bench to bedside. World J Clin Cases 2014;2(12):787–814.
26. Wenzler E, Goff DA, Humphries R, Goldstein EJ. Anticipating the unpredictable: a review of antimicrobial stewardship and Acinetobacter infections. Infect Dis Therapy 2017;6(2):149–72.

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