

Research article

# Prevalence of Tigecycline resistance in Multidrug-Resistant Acinetobacter species isolates from clinical specimens

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## ABSTRACT

**Background and Objectives:** Acinetobacter baumannii is ubiquitous, aerobic non fermentative, gram negative cocobacilli, emerging globally as an important cause of nosocomial infection. This study was conducted to determine the prevalence and antibiogram of clinically isolated multidrug-resistant Acinetobacter species.

**Material and methods:** Antibiotic susceptibility of 93 Acinetobacter baumannii isolates were performed against ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, ceftazidime, cefepime, ceftriaxone, cefotaxime, ciprofloxacin, levofloxacin, amikacin, gentamicin, imipenem, meropenem, tigecycline, polymyxin B and colistin as per standard methods in microbiology laboratory of Nepal Medicity Hospital, Kathmandu, Nepal from January to December 2018. Ethical clearance was taken from the Institutional review committee of Nepal Medicity Hospital.

**Results:** A total of 93 Acinetobacter baumannii isolates were obtained from sputum, blood, pus, wound swabs, catheter tips and others. Antibiotic susceptibility analyses of the isolates revealed that the resistance to ampicillin was most common (100%), followed by cefotaxime (75.2%), ceftazidime (74.1%), ampicillin/sulbactam (73.1%), cefepime (67.7%). However, almost all isolates were susceptible to tigecycline (100%), followed by colistin (98.9%), and polymyxin B (87.0%).

**Conclusion:** The present study showed the increasing trends of resistance of Acinetobacter species to various classes of antimicrobials. Treatment options for infections due to MDR and XDR Acinetobacter baumannii are very limited and tigecycline and colistin may be considered as one of the therapeutic options for the treatment of hospital acquired infections.

**Key words:** Acinetobacter baumannii, Antibiotic resistance, Colistin, Tigecycline,

## INTRODUCTION

Acinetobacter baumannii, the most important species of the genus Acinetobacter has emerged globally as one of the most troublesome pathogens for nosocomial

outbreak. Although associated primarily with health care associated infection, it has also been involved in cases of community acquired infections [1].

In the past these organisms were frequently ignored when isolated from clinical samples, but significant improvement in resuscitation techniques have changes the types of infections caused by Acinetobacter, which is now a serious problem [2].

Acinetobacter baumannii is a non fermentative, gram negative, oxidase negative bacilli with intrinsic resistance to commonly used antimicrobial agents [3]. These are ubiquitous organisms that can be isolated from hospital environment and survive for longer period of time on inanimate surface [4].

The isolation rate of Multidrug resistant (MDR) Acinetobacter baumannii has doubled compared to previous years and became endemic in many wards [5]. MDR Acinetobacter baumannii are responsible for many nosocomial infection outbreaks, with high morbidity and mortality, especially in critical care areas [6]. MDR Acinetobacter baumannii, defined as the isolates resistant to more than 3 classes of antimicrobial agents - all penicillins and cephalosporins including inhibitor combinations, fluoroquinolones, and aminoglycosides [6].

Carbapenems have been an effective treatment for MDR Acinetobacter infection but resistance to this class is emerging, leading to the evolution of pan-resistant strains and need for new therapeutic options [7]. Tigecycline, a new glycolcyclines, was found to have excellent in vitro activity against multidrug resistant isolates [8].

The objective of this study was to determine the prevalence of Multidrug resistance Acinetobacter baumannii and to evaluate their sensitivity towards Tigecycline, Polymixin B and Colistin.

## MATERIAL AND METHODS

A retrospective study of Acinetobacter baumannii isolates were performed in the microbiology laboratory of Nepal Medciti Hospital, Kathmandu, Nepal from January to December 2018. Ethical clearance was taken from the Institutional review committee of Nepal Medciti Hospital. The specimens were primarily processed, as per standard methods, on Blood agar, Chocolate agar and MacConkey agar. Identification of the organism was done by studying the colony morphology, Gram staining and biochemical reactions.

Antibiotic susceptibility testing by modified Kirby Bauer disc diffusion method according to CLSI (2017) guideline [9] were performed and analyzed with the following discs, ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, ceftazidime, cefepime, ceftriaxone, cefotaxime, ciprofloxacin, levofloxacin, amikacin, gentamicin, imipenem, meropenem, tigecycline, polymyxin B and colistin. Isolates were classified as multidrug resistant (MDR) and extensive drug resistant (XDR) as per reference. Briefly, the isolates showing resistance to  $\geq 1$  antimicrobial agents in  $\geq 3$  antimicrobial categories were considered as MDR and resistance to  $\geq 1$  antimicrobial agent in all but  $\leq 2$  antimicrobial categories was included as XDR [10].

## RESULTS

Over a period of 12 months, a total of 93 Acinetobacter baumannii isolates were found. The most common sample that obtained the isolates were sputum (48.3%) followed by blood (24.7%), pus (6.4%) , wound swabs (4.3%), Catheter

tip (4.3%) and others (11.8%). More of the isolates were from male (59.1%) than female (40.8%) patients. The antimicrobial susceptibility pattern of the *Acinetobacter baumannii* to various antibiotics groups is summarized in Table 1.

**Table 1: Antibiotic susceptibility pattern of *Acinetobacter baumannii* isolates**

No.	Antimicrobial agent	Sensitive (%)	Resistance (%)
1	Amikacin	51(54.8)	42(45.1)
2	Ampicillin	0(0%)	93(100%)
3	Ampicillin/sulbactam	25(26.8%)	68(73.1%)
4	Ceftazidime	24(25.8%)	69(74.1%)
5	Cefepime	30(32.2%)	63(67.7%)
6	Cefotaxime	27(29.0%)	70(75.2%)
7	Ceftriaxone	26(27.9%)	67(72.0%)
8	Ciprofloxacin	41(44.0%)	52(55.9%)
9	Colistin	92(98.9%)	1(1.0%)
10	Gentamicin	49(52.6%)	44(47.3%)
11	Imipenem	36(38.7%)	57(61.2%)
12	Levofloxacin	37(39.8%)	56(60.2%)
13	Meropenem	46(49.4%)	47(50.5%)
14	Piperacillin/tazobactam	37(39.7%)	56(60.2%)
15	Polymixin B	81(87.0%)	12(12.9%)
16	Tigecycline	93(100%)	0(0%)

## DISCUSSION

This study was conducted in Nepal Medciti Hospital and the prevalence of *Acinetobacter baumannii* among clinical isolates in our study was found to be 4.93%. This is slightly higher than a study done by Mishra et al. in Nepal [11]. The high isolation rate is a clear

indication of the emergence of *Acinetobacter* species as a serious pathogen in our region. *Acinetobacter baumannii* has emerged as one of the most resistant bacteria within the hospital environment, especially in critical care areas, which are responsible for the most severe nosocomial infections. And the high isolation rate of the pathogen has raised an alarm among the clinicians and microbiologists.

The highest numbers of *Acinetobacter baumannii* isolation in this study was from the respiratory tract samples (sputum) (48.3%), similar to a study done by Morfin et al. [12] followed by blood (24.7%), pus (6.4%), wound swabs (4.3%), Catheter tip (4.3%) and others (11.8%). More of the isolates were from male (59.1%) than female (40.8%) patients that are in accordance with the previous study [13].

In this study, *Acinetobacter* isolates demonstrate increasing resistance to commonly used antimicrobials. All 93 isolates showed 100% resistance to ampicillin that is same as a study done by Boon et al. [14]. The resistance rate to Ampicillin/sulbactam and piperacillin/tazobactam were 73.1% and 60.2% respectively. Similar type of resistance trends are also demonstrated in a study done by Shrestha et al. [15]. This can be explained by great diversity of chromosomal and plasmid mediated enzymes.

*Acinetobacter baumannii* isolates in our hospital showed high resistance rates to Cephalosporins. The rate of resistance to cefotaxime, ceftazidime, ceftriaxone and cefepime were 75.2%, 74.1%, 72.0% and 67.7% respectively. Higher resistance rate to these drugs has also been reported from a study done in Nepal by Mishra et al.<sup>11</sup> (88.7%), (82.3%), (87.1%), (85.5%), and in

Tehran by Karmostaj et al. [16] cefotaxime (96.4%), ceftazidime(96.42%) and cefepime (82.14%). The trend towards resistance to expanded spectrum cephalosporins was also demonstrated by Joly-Guillou et al and seemed to be related to the presence of cephalosporinases [17].

The resistance rate to Aminoglycosides in our study is 47.3% Gentamicin and 45.1% amikacin respectively. In contrast, Chang et al. [18] reported higher susceptibility rates (74.5%) of Amikacin among *Acinetobacter baumannii* species strains. Resistance to aminoglycosides in *A.baumannii* is mediated principally by aminoglycoside-modifying enzymes (AMEs). These include aminoglycoside phosphotransferases, aminoglycoside acetyltransferases, and aminoglycoside nucleotidyl transferases [19]. A study done by Boon et al showed high resistant to Amikacin (78.8%) and Gentamicin (85.3%) than our study [14].

In the present study, resistant to Ciprofloxacin and Levofloxacin was found in 55.9% and 60.2% of *Acinetobacter baumannii* isolates. Higher resistance to ciprofloxacin has been reported in Nepal by Mishra et al. [11] (64.52%) and in India by Joshi et al. (72.9%)[20]. Resistance to quinolones is often caused by modifications in the structure of DNA gyrase secondary to mutations in the quinolone resistance-determining regions of the *gyrA* and *parC* genes and by efflux systems that decrease intracellular drug accumulation [19].

Carbapenems were used to treat MDR *Acinetobacter* infections, but carbapenem resistant *Acinetobacter baumannii* have been increasing worldwide and decreased the effectiveness of these agents. We found much higher resistance rate of the isolates towards

the carbapenems i.e 61.2% and 50.5% to imipenem and meropenem respectively. Similar type of resistance pattern has been reported from Nepal by Mishra et al.[11] (50% for meropenem and 35.48% for imipenem) and Manikal et al. [21] observed a high rate of resistance, 50% to imipenem and 51% to meropenem. The resistance to  $\beta$  lactam antibiotics including carbapenems is acquired mainly by reduced outer-membrane permeability and increased AmpC beta-lactamase production [7].

Nevertheless, carbapenems are still considered as one of the treatment options for MDR *Acinetobacter baumannii*, which retains sensitivity to carbapenems. For carbapenem-resistant *Acinetobacter baumannii*, tigecycline and colistin are 2 of the most frequently used alternative agents according to the literature [22].

Colistin and polymyxin B have also been used as an alternative to treat highly resistant *Acinetobacter* infections [23]. Resistances to Colistin and polymyxin B have also been reported in literature [21]. In our study resistant to Colistin and Ploymixin B found is (1%) and (12.9).

Furthermore, the evolvement of both MDR and XDR *Acinetobacter baumannii* has been reported by Kempf and Rolain in 2012 [24]. Dent et al. reported 72% and 58% MDR and XDR, respectively, among *Acinetobacter baumannii* in their study [25].

The results from the present study also showed majority of the isolates to be MDR, whereas >50% of them showed XDR against the tested antibiotic groups. The exhibition of high levels of MDR and XDR by *Acinetobacter baumannii* isolates has been reported in different regions of the world.

In our study, all 100% of isolates were sensitive to Tigecycline followed by colistin 98.9% and polymixinB 87.0%. Tigecycline and Colistin remain the only active antibiotics and have become the last resort of treatment options for the management of infections caused by multidrug resistant *Acinetobacter baumannii* strains [26].

## CONCLUSION

From the results of the present study, it can be concluded that treatment options for infections due to MDR and XDR *Acinetobacter baumannii* are very limited and tigecycline may be considered as one of the therapeutic option for the treatment of hospital acquired infections. Implementation of infection control measures and antibiotic control strategy in hospital is needed to prevent multidrug resistance by regular analysis of antibiogram of *Acinetobacter* species. So that effective empirical drug regimen can be applied to prevent drug resistance and thus the morbidity and mortality.

It can be recommended from the study that proper antibiotic stewardship program should be incorporated so that effective empirical drug regimen can be applied to prevent multidrug resistance.

## ACKNOWLEDGEMENTS

Authors would like to thank all the staff from Department of Microbiology Laboratory for their support in conducting this study.

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