### **Original Article**

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## Multidrug-resistant *Acinetobacter* septicemia in neonates: A study from a teaching hospital of Northern India

Asifa Nazir

#### Abstract:

**BACKGROUND:** Acinetobacter species are typical nosocomial pathogens causing infections and high mortality, almost exclusively in compromised hospitalized patients. Acinetobacter sp. are intrinsically less susceptible to antibiotics and have propensity to acquire resistance. Multidrug-resistant (MDR) Acinetobacter sp. blood infection in the neonatal intensive care unit patients create a great problem in hospital settings.

AIMS: A prospective data analysis was performed over a one year period of all neonates admitted with sepsis who developed *Acinetobacter* infection and their antibiotic susceptibility pattern was carried out.

**MATERIALS AND METHODS:** Blood samples of infected neonates were collected aseptically and cases of *Acinetobacter* septicemia were identified. Speciation of *Acinetobacter* species was done. Various risk factors were identified and their drug-sensitivity test was performed.

**RESULTS:** The incidence of neonatal septicemia due to *Acinetobacter* species was 13.7% (49/357). Predominant species isolated was *Acinetobacter baumannii* (98%). The major symptoms were lethargy and poor feeding. The major signs were tachypnea, intercostal retraction, and respiratory distress. The major fetal risk factors were low birth weight and prematurity. High degree of resistance was observed to the various antibiotics used. Majority of the isolates (95.9%) were MDR while 93.68% were resistant to carbapenems as well as extensively drug resistant. However, all the strains were sensitive to colistin.

**CONCLUSION:** MDR *Acinetobacter* septicemia in neonatal patients is becoming alarmingly frequent and is associated with significant mortality and morbidity. Therefore, rational antibiotic use is mandatory along with an effective infection control policy in neonatal intensive care areas of each hospital to control *Acinetobacter* infection and improve outcome.

#### Key words:

Acinetobacter septicemia, blood culture, multidrug resistance, neonatal sepsis

### Introduction

A cinetobacter species are aerobic Gram-negative, catalase-positive, oxidase-negative coccobacilli which were first described in 1911.<sup>[1]</sup> Members of the genus *Acinetobacter* are ubiquitous, free-living organisms that prefer moist environment and can be easily obtained from soil, water, food, and sewage.<sup>[2]</sup> They are nonfermentative organisms that have

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emerged as significant nosocomial pathogens in the hospital setting and are responsible for intermittent outbreaks.<sup>[3]</sup> According to the National Neonatal Perinatal Database 2000, the incidence of neonatal septicemia in India has been reported to be 24/1000 per live births. *Acinetobacter* sp. are gaining importance as a potential pathogen in neonatal septicemia because of its frequent isolation and multidrug resistance (MDR).<sup>[4]</sup> *Acinetobacter* species are the second most commonly isolated nonfermenter organisms in human specimens (*Pseudomonas aeruginosa* 

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Department of Microbiology, Government Medical College, Srinagar, Jammu and Kashmir, India

### Address for correspondence:

Dr. Asifa Nazir, 370 BBC, Shivpora, Srinagar - 190 004, Jammu and Kashmir, India. E-mail: asifanazir@gmail. com

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is the most common).<sup>[5]</sup> They rank fourth (after *P. aeruginosa, Staphylococcus aureus,* and *Klebsiella pneumoniae*) among the most frequent hospital-acquired infectious agents.<sup>[6]</sup>

According to the Centers for Disease Control and Prevention (CDC), the species *Acinetobacter baumannii* accounts for nearly 80% of reported *Acinetobacter* infections.<sup>[7]</sup> *A. baumannii* has become an increasingly frequent cause of healthcare-associated infections (HAIs), particularly in intensive care units (ICUs).<sup>[8,9]</sup>

Prior antibiotic use, prolonged hospitalization, colonization pressure, and enteral feeding have all been implicated in risk of *Acinetobacter* infection.<sup>[10,11]</sup> In recent years, *Acinetobacter* has been increasingly recognized as a significant healthcare-associated, opportunistic, MDR pathogen, and the rate of isolation has increased since the last two decades worldwide with a high morbidity and a high mortality rate, especially in immunocompromised patients ranging from 26.5% to 91%.<sup>[3,12]</sup>

Prolonged survival in the healthcare environment–along with MDR – colonization potential, and contact transmission (hands, instruments, and equipment) – is some of the challenging factors in *Acinetobacter* prevention and control.<sup>[13]</sup>

Antimicrobial resistance among *Acinetobacter* species has increased substantially in the past decade.<sup>[14]</sup> The capacity of *Acinetobacter* species for extensive antimicrobial resistance may be due in part to the organism's relatively impermeable outer membrane and its environmental exposure to a large reservoir of resistance genes.<sup>[15]</sup> Further, carbapenem resistance is increasingly reported and has become a significant public health concern.<sup>[16,17]</sup>

Different terms such as "MDR," "extensive drug resistant (XDR)," and "pandrug resistant (PDR)" have been used with varied definitions to describe the extent of antimicrobial resistance among *Acinetobacter* sp., but there is no accepted definition for the extent of resistance in the bacteria.<sup>[18,19]</sup>

A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control<sup>[20]</sup> and the CDC, to create a standardized international terminology with which to describe acquired resistance profiles in *S. aureus, Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *P. aeruginosa*, and *Acinetobacter* spp., all bacteria often responsible for HAIs and prone to MDR. MDR was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and PDR was defined as nonsusceptibility to all agents in all antimicrobial categories. A review was recently published<sup>[21]</sup> in which the definitions were proposed for grading various antimicrobial resistance profiles.

In the present study "MDR *Acinetobacter* sp." would be defined as the isolate resistant to at least three classes of antimicrobial agents such as all penicillins and cephalosporins (including inhibitor combinations), fluroquinolones, and aminoglycosides. "XDR *Acinetobacter* spp." would be the *Acinetobacter* sp. isolate that is resistant to the three classes of antimicrobials described above (MDR) and shall also be resistant to carbapenems. Finally, "PDR *Acinetobacter* spp." would be the XDR *Acinetobacter* spp. that is resistant to polymyxins and tigecycline.<sup>[22]</sup>

Since very few studies have been published on bacteremia caused by *Acinetobacter* species in our region, this study was undertaken to determine the incidence and antibiotic resistance pattern of *Acinetobacter* species isolated from blood samples of neonatal septicemia patients.

### Materials and Methods

This prospective study was conducted in the Department of Microbiology of a teaching hospital of Northern India over a period of 1 year. The study was approved by the ethical committee of our institute. All blood culture positive for *Acinetobacter* sp. and their *in vitro* sensitivity to antibiotics were included from March 2017 to February 2018. Bacteremia was defined as the presence of *Acinetobacter* sp. in one or more blood cultures from a patient during hospitalization.

Blood was collected from suspected cases of neonatal sepsis by maintaining strict aseptic precaution in blood culture bottles and sent immediately to Microbiology Laboratory. Blood specimens were cultured using BacTAlert3D (BioMerieux, India®) automated blood culture system. 1 ml of blood was inoculated into ready to use BacT/ALERT PF Plus culture bottles (yellow coded) for pediatric use with all due precautions and shaken well. Positive or negative culture bottles were determined by BacT/ALERT microbial detection system. Blood cultures were considered negative only after 7 days of incubation.

Gram stain was carried out on positive bottles, followed by inoculation onto blood agar and MacConkey agar plates, and incubated aerobically for 24 h at 37°C. Identification was carried up to species level, and antimicrobial susceptibility testing was done with an automated microbiology system (Vitek 2 Compact 60 System, BioMerieux India<sup>®</sup>) and interpreted according to the Clinical and Laboratory Standards Institute criteria.<sup>[23]</sup> The patient's data that were collected included age, sex, underlying diseases, and risk factors. Quality control was performed by testing these same antimicrobials against reference strains of bacteria.

Statistical analysis was done to see the association between various risk factors and *Acinetobacter* septicemia.

#### Results

A total of 357 blood culture samples were consecutively included in the study. *Acinetobacter* sp. was isolated from 49 (13.7%) samples out of which 48 (98%) were *A. baumannii*, 1 (0.02%) was *Acinetobacter lwoffii*.

Among 357 cases included in the study, the male-to-female ratio was 2:1. The gestational age was <36 weeks in 38 (77.5%) cases and low birth weight babies were 40 (81.6%).

The main risk factors associated with *Acinetobacter* septicemia were low birth weight (81.6%), prematurity (77.5%), prolonged intravenous antibiotic use (75.5%), mechanical ventilation (46.9%), and prolonged hospital stay (44.8%) [Table 1].

The major signs and symptoms included poor feeding/activity (81.6%) followed by respiratory distress (57.1%), convulsions (12.2%), and fever (12.2%). Jaundice was seen in 6.12% and abdominal distension in 4.08% cases [Table 2].

Antibiotic-susceptibility pattern was studied among the *Acinetobacter* isolates [Table 3]. High degree of resistance was observed to the various antibiotics used.

Majority of the isolates (95.9%) were MDR, i.e., resistant to penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones, and aminoglycosides while 93.68% were resistant to carbapenems as well (XDR). Minocycline resistance was seen in 69.3% cases while tigecycline resistance was observed in 6% cases. However, all the strains were sensitive to colistin [Table 4].

### Discussion

Over the last three decades, *Acinetobacter* species has emerged as an important pathogen in the healthcare setting, both globally and locally. It has remarkable ability to develop or acquire multiple antibiotic resistance and propensity to survive for prolonged periods under a wide range of environmental conditions, making it a

### Table 1: Potential risk factors identified in cases of Acinetobacter septicemia neonates (n=49)

Risk factors	Number of cases (%)	
Low birth weight	40 (81.6)	
Prematurity	38 (77.5)	
Prolonged IV antibiotics	37 (75.5)	
Ventilator support	23 (46.9)	
Prolonged NICU stay (>7 days)	22 (44.8)	

IV = Intravenous, NICU = Neonatal intensive care unit

### Table 2: Clinical presentations observed in cases of Acinetobacter septicemia neonates (n=49)

Number of cases (%)
40 (81.6)
28 (57.1)
6 (12.2)
6 (12.2)
3 (6.12)
2 (4.08)

### Table 3: Susceptibility pattern of Acinetobacter spp.to different antimicrobial agents (n=49)

Antibiotic	Sensitive (%)	Resistant (%)
Ceftriaxone	0 (0)	49 (100)
Cefepime	0 (0)	49 (100)
Gentamicin	2 (4.08)	47 (95.9)
Ciprofloxacin	2 (4.08)	47 (95.9)
Imipenem	3 (4.08)	46 (93.8)
Meropenem	2 (4.08)	47 (95.9)
Piperacillin + tazobactam	1 (2.04)	48 (97.9)
Ceftriaxone + sulbactam	2 (4.08)	47 (95.9)
Ampicillin	0 (0)	49 (100)
Amoxicillin clavulanic acid	0 (0)	49 (100)
Minocycline	15 (30.6)	34 (69.3)
Tigecycline	43 (87)	6 (12.2)
Colistin	49 (100)	0 (0)

# Table 4: Rate of multidrug-resistant, extensive drug-resistant and pan drug-resistant *Acinetobacter* spp. (*n*=49)

Categories of Acinetobacter	Definition	n (%)
MDR	Resistant to three groups	47 (95.9)
	Penicillins and cephalosporins (including inhibitor combinations)	
	Fluoroquinolones	
	Aminoglycosides	
XDR	MDR + resistant to carbapenems	46 (93.8)
PDR	XDR + resistant to polymyxin E (colistin)	0

MDR = Multidrug resistant, XDR = Extensive drug resistant, PDR = Pan drug resistant

frequent cause of hospital outbreaks and an endemic healthcare-associated pathogen. It commonly targets the most vulnerable hospitalized and critically ill patients with breaches in skin integrity who require airway protection, causing pneumonia, urinary tract infection, wound infection, and bacteremia.<sup>[9-11]</sup> MDR nosocomial *Acinetobacter* sp. septicemia may cause severe clinical diseases in neonate that is associated with a high mortality.<sup>[22]</sup>

The present study was undertaken to find the incidence of *Acinetobacter* septicemia in neonates and its antibiotic resistance pattern.

In our study, the *Acinetobacter* sepsis incidence was 13.7%. This percentage was similar to the studies which were conducted by Vinodkumar and Neelagund<sup>[4]</sup> (8.3%), Arora and Jaitwani<sup>[24]</sup> (12.3%), and Mondal *et al.* (15.2%).<sup>[25]</sup> *A. baumannii* was the predominant species in our study (98%). In other studies, also, the main species responsible for neonatal sepsis was *A. baumannii*.<sup>[25]</sup> This percentage was however higher than the percentage in the study which was conducted by Arora and Jaitwani, (56.52%).<sup>[24]</sup> Female sex was affected more commonly with ratio of 1.6:1 in our study which is similar to the finding by Christo *et al.*<sup>[26]</sup>

In our study, Acinetobacter sepsis was found more in premature (77.5%) and very low birth weight babies (81.6%) which is similar to findings from other studies.<sup>[24,27,28]</sup> Preterm infants have a 3-10-fold higher incidence of infection than full-term infants as they often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry for infection.<sup>[29-32]</sup> Outbreaks of Acinetobacter infection have been traced to medical equipment, emphasizing the need for special attention to disinfection of shared items and extra caution with respiratory care and wound care procedures.<sup>[33]</sup> In our study, a significant association between Acinetobacter bloodstream infection and prolonged ICU stay was noted. Acinetobacter spp. has the reputation of causing outbreaks in ICUs.<sup>[34]</sup> It indirectly predicts that the isolate is of hospital origin and poses a great threat for the neonate and rises a concern in the management. The organism can survive on environmental surfaces for months, making nosocomial transmission extremely difficult to prevent and control.<sup>[35]</sup>

MDR *Acinetobacter* has been reported worldwide and is now recognized as one of the most difficult HAIs. Mechanisms of acquiring resistance to cephalosporins and carbapenems described for *A. baumannii* are altered penicillin-binding proteins, presence of metallo-beta lactamases, and loss of porins.<sup>[15,16]</sup>

Acinetobacter strains isolated during our study exhibited MDR pattern. 95.9% strains were MDR, i.e., resistant to penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones, and aminoglycosides, while 93.68% were resistant to carbapenems as well (XDR). A study conducted in New Delhi, India (2006), revealed that the prevalence of carbapenem resistance in *Acinetobacter* spp. isolated from different clinical samples was found to be almost 35%.<sup>[36]</sup> Further, Gladstone *et al.* from Vellore, India (2005), reported a prevalence of 14% carbapenem-resistant *Acinetobacter* spp., isolated from tracheal aspirates (n = 56).<sup>[37]</sup> In a surveillance study of the antibiotic susceptibility patterns of the isolates from the ICUs of five European countries (1999), the prevalence of resistance in *Acinetobacter* spp. to gentamicin was 0%–81%, amikacin 10%–51%, ciprofloxacin 19%–81%, ceftazidime 0%–81%, piperacillin-tazobactam 36%–75%, and imipenem 5%–19%.<sup>[38]</sup>

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) program reported the antimicrobial susceptibility of 490 *A. baumannii* strains collected in 37 centers in 11 European countries from 1997 to 2000.<sup>[39]</sup>

Imipenem and meropenem were found as the most active agents against *A. baumannii*, with resistance rates of 16 and 18%, respectively.

Subsequent data from 40 centers in 12 countries participating in the MYSTIC program (2006) revealed a substantial increase in resistance rates for meropenem (43.4%) and imipenem (42.5%).<sup>[40]</sup>

Data of the antibiotic susceptibilities of *Acinetobacter* from different geographical regions revealed that the resistance of *Acinetobacter* spp. to imipenem rose from no resistance to 40% (2000–2004).<sup>[41]</sup> The prevalence of imipenem resistance in *A. baumannii* isolated from a burns unit of the USA was found to be as high as 8% (2007).<sup>[42]</sup> Resistances to major antimicrobial drugs as well as disinfectants are the major factors that make it a successful and persistent hospital pathogen.<sup>[30]</sup>

Many neonates in hospitals in India are now treated with carbapenems as a first-line therapy for sepsis or presumed sepsis. Against this backdrop, the widespread availability and antimicrobial use in community settings and the contribution of antimicrobial resistance as a complicating factor in neonate sepsis become extremely important.

In the present study, minocycline resistance was seen in 69.3% cases while tigecycline resistance was observed in 6% cases. Tigecycline is a minocycline derivative with enhanced *in vitro* activity against both Gram-positive and Gram-negative bacteria, including *A. baumannii*. However, clinical data in treating *A. baumannii* infections remain limited. Breakthrough bacteremia by *A. baumannii* in patients receiving tigecycline has also been reported.<sup>[43]</sup> It is important to note that the emergence of tigecycline resistance may occur while the patient is on treatment.<sup>[44]</sup> All the strains that we tested were sensitive to colistin. This is likely due to the fact that colistin has been limited from being used during the last several decades due to nephrotoxicity. At present, the therapeutic options for infections caused by antibiotic-resistant strains of *A. baumannii* are limited. This indicates that we should be judicious in use of antibiotics while treating *Acinetobacter* infections.

*Acinetobacter* sp. are rapidly spreading with emergence of extended resistance to even newer antimicrobials. They have the ability to acquire resistance at a much faster than another Gram-negative organism.<sup>[22]</sup> Due to their ease of survival in the hospital environment, they have immense potential to cause nosocomial outbreaks. The global emergence of MDR *A. baumannii* has reduced the number of clinically available antibiotics that retain activity against this pathogen. For this reason, the development of novel treatment strategies for infections caused by *A. baumannii* is necessary.

### Conclusion

Because of the tremendous challenge posed by MDR *A. baumannii* and the emergence and dissemination of mechanisms of resistance to any existing agent, solutions beyond the paradigm of antibiotics should be explored aggressively.<sup>[45]</sup> Infection control is extremely important especially given the ability of *A. baumannii* to cause outbreaks. Contact precautions, hand-washing, and alcohol-hand decontamination, although universally encouraged, are seldom applied rigorously. Their importance, however, cannot be overstressed.<sup>[46]</sup>

There is an urgent need to enforce infection control measures and antimicrobial stewardship programs to prevent the further spread of these resistant *Acinetobacter* species and to delay the emergence of increased resistance in the bacteria.

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### **Conflicts of interest**

There are no conflicts of interest.

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