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RETROSPECTIVE ANALYSIS OF BLOOD STREAM INFECTIONS CAUSED BY *ACINETOBACTER SPECIES* AND ANTIBIOTIC SUSCEPTIBILITY PATTERN IN A TERTIARY CARE CENTER OF BIHAR

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Abstract–*Acinetobacter baumannii* (*A.baumannii*), one of the most important representatives of *Acinetobacter spp.* has emerged as an important pathogen for hospital acquired infections like bacteremia, pneumonia, urinary tract infections, and skin and soft tissue infections mainly affecting critically ill patients. *Acinetobacter spp.* has an enhanced ability to survive and spread in hospital environments among patients and healthcare workers. Currently, most of the strains of *A. baumannii* are multidrug-resistant. These characteristics make Acinetobacter infections difficult to treat and prevent. Blood stream infections (BSIs) are an important cause of mortality and morbidity among patients admitted in hospitals and they constitute a major portion of all hospital acquired infections. *A. baumannii* has emerged in the last decades as an important pathogen causing BSIs especially in ICUs among patients with ventilator support or central line and has high mortality and morbidity. Taking into consideration these facts, the study was aimed to investigate the prevalence of *Acinetobacter spp.* blood stream infections and to figure out their current antimicrobial susceptibility pattern so that clinicians could be guided about proper empirical antimicrobial treatment. This retrospective study was conducted in the Dept. of Microbiology, AIIMS, Patna. Laboratory and Hospital records were analyzed for all the blood samples collected from admitted patients during the period of September 2018 to August 2019. All the blood samples had been processed by standard microbiological procedures for bacteriological identification and antimicrobial susceptibility testing. Data were plotted and statistical analysis was done using Microsoft Excel Sheet (V. 2007). The overall prevalence of *Acinetobacter spp.* among blood cultures was found to be 2.3%. Patients less than 30 years of age including the pediatric age group constitute a major portion of cases (53.6%) with a male predominance. Patients admitted in various ICUs contributed a major portion (47.8%) of cases of Acinetobacter bacteremia. Colistin showed the best sensitivity (72.2%) followed by Imipenem (68.7%) and Levofloxacin (66.7%). The isolates showed the most resistance to Amoxycillin (80%) followed by Amikacin (70%) and Ceftriaxone (69.6%). *Acinetobacter spp.* has become an important pathogen causing BSIs especially in ICUs and involves patients not only from the older age groups but also young adults and pediatric age groups. Most of the commonly used antibiotics like Penicillin and other Cephalosporins and even aminoglycosides have become ineffective in treating such infections due to high resistance rates. Carbapenems and Colistin remain the most effective drugs but also demand their judicious use as resistance has started to emerge.

INTRODUCTION

Acinetobacter species, which are lactose non-fermenting, Gram negative coccobacillus, are a diverse group of organisms, and *A. baumannii*, the most important representative species of the genus, has emerged globally as a major cause of healthcare associated infections. It can cause various infections, including bacteremia, pneumonia, meningitis, catheter-related bloodstream infections, intra-abdominal infections, urinary tract infections, and skin and soft tissue infections mainly affecting patients with impaired host defenses in the intensive care unit (ICU) setting (Bergogne-Berezin and Towner, 1996).

Acinetobacter spp. is resilient to the environment and has the ability to survive in hospital environments and the hands of health care workers which results in the clonal spread of isolates and makes *Acinetobacter spp.* easy to transmit from one to

another person. Another concern associated with *Acinetobacter spp.* is their ability to rapidly acquire resistance determinants, leading to multidrug resistance. This phenomenon makes it difficult to treat Acinetobacter infections in the current antibiotic era (Maragakis and Perl, 2008; Peleg *et al*., 2008; Joly-Guillou, 2005).

Acinetobacter spp. emerged as an important infectious agent during the 1960s and 1970s due to an increase in invasive treatment produces (Glew *et al.,* 1997; Daly *et al*., 1962).

In a hospital environment *A. baumannii* can spread through aerosols and its infections are associated with Mechanical ventilation, intravascular and urinary catheterizations, invasive surgical procedures, prolong use of broad-spectrum antibiotics, mostly in trauma and burn ICUs (Maragakis and Perl, 2008; Joly-Guillou, 2005; Chopra *et al*., 2014).

Blood stream infections (BSIs) remain one of the foremost important causes of morbidity and mortality globally. The infection may range from self-limiting to life-threatening sepsis (Dagnew *et al*., 2013; Gohel *et al.*, 2014).

A. baumannii bloodstream infections typically occur in the presence of a central venous catheter or secondarily due to extensive pneumonia, facilitating dissemination and it has a very high mortality rate in case of infection is caused by an MDR isolate (Lee *et al.,* 2014).

Studies done by different authors' shows that *A. baumannii* isolates form patient with nosocomial blood stream infection are resistant to various different groups of commonly used antimicrobials like Ampicillin (>74%), Cefotaxime (d"65%), Piperacillin/tazobactam (d"80%),Imipenem (d"70%) and Ciprofloxacin (d"80%) (Wisplinghoff *et al*., 2000; Swamy *et al*., 2018).

A study conducted by Surbhi et al. and others showed an increase in blood stream infections caused by *Acinetobacter spp.* especially in hospital settings in recent years. Surbhi et al. demonstrated in their study that the prevalence of *Acinetobacter spp.* in blood stream infections from hospitals of Northern India increases from 20% to 30% during the period of the year 2013 to 2016 (Khurana *et al*., 2018).

A study done by Lee *et al.* (2010) shows that the economic burden increases sharply with the length of hospital stay in patients with Acinetobacter infections (Lee *et al*., 2010).

The crude mortality of *A. baumannii* bloodstream infection (BSI) may be as high as 52% (Beck-Sague *et al*., 1990; Cisneros *et al*., 1996).

From the above discussion, it has been established that *Acinetobacter spp*. is an important emerging pathogen, especially for Hospital Acquired Infections.

The purpose of this study is to investigate the prevalence of *Acinetobacter spp.* blood stream infections and to figure out their current antimicrobial susceptibility pattern so that clinicians could be guided about proper empirical antimicrobial treatment and minimizing ineffective antimicrobials use, mortality and morbidity, and burden of health care cost by reducing the length of hospital stay.

MATERIALS AND METHODS

This is a retrospective study conducted in the department of microbiology, at AIIMS, Patna, a tertiary care center in Bihar after getting the approval of the Institutional Ethical Committee (AIIMS/Pat/IEC/2019/396). Microbiological data of all the blood samples from admitted patients sent for culture and sensitivity tests during the period of September 2018 to August 2019 were analyzed. The data were obtained from Laboratory and Hospital records.

The blood samples which were analyzed were sent to the laboratory for blood culture and sensitivity testing from patients suspected of bacteremia or sepsis with the relevant clinical history and demographic details of the patient. Blood culture bottles from Biomerieux were inoculated with the sample and incubated in BACT/ALERT 3D. When the instrument signaled positive, subcultures were done on blood agar, MacConkey agar, and chocolate agar. The growth obtained was identified by colony morphology, Gram stain of the isolated colonies, standard microbiological and biochemical tests. Non-lactose fermenting colonies were tested for Cytochrome Oxidase activity by using Oxidase disc from Hi-media (Mumbai). Those isolates which were found negative on the Oxidase test were further evaluated using different biochemical tests like Nitrate reduction, Indole production, Motility on semisolid agar, Citrate utilization test, Urease production, and TSI reactions.

The antibiotic susceptibility pattern of the isolated organisms was performed by Kirby-Bauer disc diffusion method on Mueller-Hinton agar

plates according to CLSI guidelines 2017(Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 2017). The following antibiotics were tested–Ceftazidime, Ciprofloxacin, Levofloxacin, Imipenem, Meropenem, Gentamicin, Amikacin, Piperacillin-tazobactam, Cefepime, Cefotaxime, Ceftriaxone and Tetracycline, Co-trimoxazole, Cefoperazone-Sulbactam.

The statistical calculations and related graphs will be done using MS Excel Sheet 2007.

RESULTS

During this retrospective study, we evaluated a total number of 2946 samples of blood culture processed in the duration of 1 year and found 69 isolates (2.3%) of *Acinetobacter spp.* The samples were collected from patients of all age groups and the most common age group was < 10 years (26, 37.68%) followed by 21-30 years (11, 15.9%). We find a male: female ratio of 2:1 (46:23) which shows a male predominance (Table 1, Fig. 1).

Table 1. Age and Sex distribution of patients

Age	Male	Female	Total
<10	19	7	26
11-20	7	1	8
21-30	6	5	11
31-40	4	1	5
41-50	4	2	6
51-60	4	5	9
61-70	2	2	4
Total	**46**	**23**	**69**

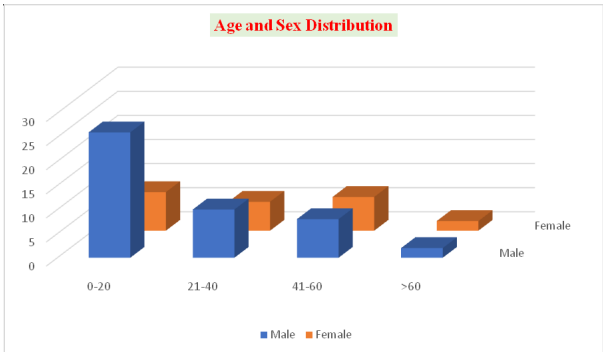

Fig. 1. Age and Sex distribution of patients

We find that most of the Acinetobacter isolates were from Trauma ICU (14, 20.3%) follow by Pediatric ICU (13, 18.8%) and Surgery ward (8, 11.6%) (Table 2, Fig. 2).

Table 2. Ward wise distribution of patients

Ward	Male	Female	Total
TICU	9	5	14
NICU	3	3	6
PICU	13	0	13
Surgery Ward	5	3	8
HDU	2	2	4
Medicine Ward	4	1	5
OBG Ward	1	2	3
Trauma Ward	3	3	6
Pulmonary Ward	0	1	1
Ayush	1	0	1
Neuro surgery	0	1	1
OPD	0	1	1
Pediatric Ward	1	0	1
Dermatology Ward	0	1	1
Paed. Surg. Ward	1	0	1
Others	3	0	3
Total	46	23	69

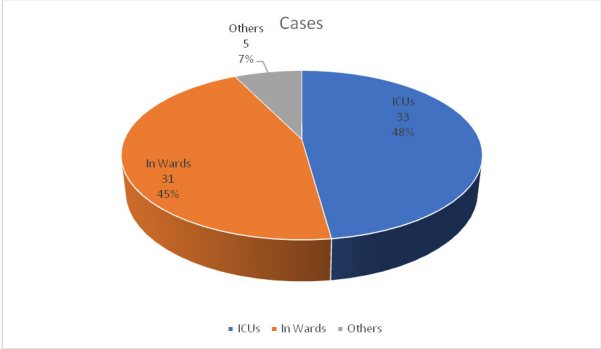

Fig. 2. Ward wise distribution of patients

Colistin showed the best sensitivity (72.2%) follow by Imipenem (68.7%), Levofloxacin (66.7%), and Cefoperazone (66.1%). The isolates showed the most resistance to Amoxycillin (80%) follow by Amikacin (70%), Ceftriaxone (69.6%), and Gentamicin (62.2%) (Table 3, Fig. 3).

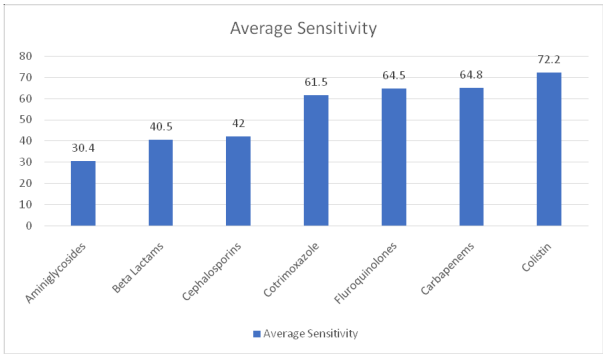

Fig. 3. Antibiotic susceptibility pattern of the isolates

Table 3. Antibiotic susceptibility pattern of the isolates

Antibiotic	Sensitive (%)	Resistant (%)	Intermediate (%)
Amoxycillin	20	80	0
Cefepime	36.36	60	3.37
Cefoperazone-Sulbactum	66.10	25.42	8.47
Ceftriaxone	21.74	69.56	8.69
Aztreonam	42.85	50	7.14
Ceftazidime	43.64	56.36	0
Gentamicin	33.33	62.22	4.45
Amikacin	27.5	70	2.5
Ciprofloxacin	62.29	34.42	3.28
Levofloxacin	66.66	33.33	0
Piperacillin-Tazobactum	58.73	38.09	3.18
Imipenem	68.66	29.85	1.49
Meropenem	60.78	39.21	0
Cotrimoxazole	61.53	36.53	1.93
Colistin	72.22	27.78	0
Tetracyclin	58.33	41.67	0

DISCUSSION

The prevalence of *Acinetobacter spp.* in this study in blood samples was found to be 2.3% (69/2946). Studies conducted by various authors found it more than 7% which is much greater than the current study (Banerjee *et al*., 2018; Kaur *et al*., 2018).

The difference may be due to the fact that those studies focus on ICU patients only whereas this study includes patients from all indoor wards and OPDs.

Children and young adults (<30 years of age) contribute most of the cases, i.e. 53.6%. This is in contrast to studies done by other authors where the mean age was around 50 years (Al Samawi *et al.*, 2016; Huang *et al*., 2018).

This may be due to the fact that patients less than 30 years of age constitute the majority of the cases in this study and studies done by various authors showed an increase in *Acinetobacter spp.* infections among the pediatric population in the hospital environment (Logan *et al*., 2019; Jain *et al.*, 2016).

Male predominance was seen in this study with the ratio of male and female patients more than 2. This is in harmony with studies conducted by Qiao L et al. and Banerjee et al. where the male: female ratio varies from 1.7 to 2.3 (Banerjee *et al.*, 2018; Qiao *et al.,* 2016).

ICUs are the most important sites for Acinetobacter infections including BSIs and studies done by various authors showed that the majority of the cases were from various ICUs. A study conducted by Sileem *et al.* (2017) showed a statistically significant difference in Acinetobacter infections in ICUs comparison to other wards in hospitals (Sileem *et al*., 2017).

Another study conducted by Murugesh *et al.* (2020) also showed that 33.7% of all Acinetobacter infections were from ICUs.

The higher incidence may be due to presence of various risk factors present in ICU patients like mechanical ventilation, catheterization, surgical procedures, presence of various co-morbidities, and use of broad-spectrum antibiotics (García Garmendia *et al.*, 2001; Ellis *et al*., 2015).

The antimicrobial resistance pattern of *Acinetobacter spp*. varies widely and most of the strains are multi-drug resistant. In this study, the average sensitivity for Aminoglycosides, one of the most commonly used antibiotic groups for Acinetobacter infections were 30.4%. This is in harmony with a study done by Murugesh *et al*. in 2019 where the sensitivity for Gentamicin was 34.5% and Amikacin showed a better sensitivity with 58.2% (Murugesh *et al*., 2020).

Another study by Al Samawi *et al*. in 2016 showed a better sensitivity for both Amikacin and Gentamicin with 67.5 and 53.9% sensitivity (Al Samawi *et al.*, 2016).

While this shows an increase in resistance over the years but another study conducted by Kumari *et al.,* 2019 showed that the resistance of *Acinetobacter spp*. over 5 years from 2012 to 2016 has decreased slightly for aminoglycosides from more than 90% (96.8%) to near 80% (84.5%).

A study conducted by Veeraraghavan *et al.* 2009 in 2019 on "GLASS pathogens"showed that the sensitivity of Amikacin for *Acinetobacter baumannii* isolates was 15-61%.

This result corresponds to the current study. This current study along with other previously conducted studies establishes the fact that *Acinetobacter spp*. isolates can vary in their sensitivity towards Aminoglycosides in a wide range of sensitivities.

A similar wide range of variability in antimicrobial sensitivity is also shown by other classes of antibiotics like Ceftazidime (0-79%) and Piperacillin-Tazobactum (10-66%) (Veeraraghavan and Walia, 2019).The results correspond to the current study where the sensitivities for those antibiotics fell in those ranges.

Acinetobacter spp. shows extensive resistance to

few classes of antibiotics like b-Lactams, Cephalosporins, and Fluroquinolones. Studies conducted by various authors showed that resistance for Cephalosporins and Fluroquinolones can vary in wide ranges i.e. >80%-96% (Murugesh *et al*., 2020; Veeraraghavan and Walia, 2019).

In the present study, Cephalosporins showed overall poor sensitivitywhile Fluroquinolones showing better susceptibility for *Acinetobacter spp.* isolates. This is in harmony with a study conducted by Prashanth and Badrinath, (2004), where the susceptibility of Cefotaxime and Ciprofloxacin was 6.2 and 37.5% respectively (Prashanth and Badrinath, 2004).

Carbapenems like Imipenem and Meropenem are considered preferable drugs for serious infections like bacteremia caused by *Acinetobacter spp.* (Fishbain and Peleg, 2010).

In recent years there has been a steady increase in Carbapenem-resistant strains of *Acinetobacter spp.* (CRAB). which makes treatment of such infections more challenging (World Health Organization. Central Asian and Eastern European Surveillance of antimicrobial resistance, 2017). A study conducted by Veeraraghavan *et al.* in (2019), showed the sensitivity for Imipenem ranges from 20%- 71% and for Meropenem 10-73% in India. Studies conducted by Kumari M *et al.* from 2012 to 2016 found a similar resistance pattern for Carbapenems with average resistance for Imipenem and Meropenem was 90% (Kumari *et al*., 2019).

This is in contrast to this current study where authors have found much higher sensitivity for carbapenems (average sensitivity 64.8%). However, the findings of the current study are in harmony with a study conducted by Al Samawi *et al.* during 2012 to 2013 where the resistance for Imipenem was 35.1% and Meropenem was 45.6% (Al Samawi *et al.*, 2016).

This shows the rapid emergence of carbapenem resistance among *Acinetobacter spp*. which is mostly mediated by class D carbapenemase blaOXA-23-like (42-99%) (Khajuria *et al*., 2014).

Serious infections like blood stream infections by such resistant strains have a grave effect on mortality and morbidity and increase the economic burden of healthcare (Lemos *et al*., 2014; Zhen *et al.*, 2020).

Laboratory detection of such resistant strains is of utmost importance in guiding the antimicrobial therapy and also preventing the spread of such stains in healthcare institutes as a part of institutional infection control practices (Corrêa *et al*., 2012; Cheon *et al*., 2016).

In this current study, Colistin showed the highest sensitivity (72.2%) against the *Acinetobacter spp.* isolates. This is in harmony with a study conducted by Veeraraghavan *et al.* where the sensitivity was found to be 78-100% (Veeraraghavan and Walia, 2019). A previous study conducted by Samawi *et al*. (2016) during 2012-2013 found Colistin extremely effective against Acinetobacter strains with resistance among 1.4% of isolates (Al Samawi *et al*., 2016). Colistin which is often considered as last resort drugs for such MDR pathogens should also be used cautiously because of the emerging resistance among *Acinetobacter spp.* isolates. Such resistance can also occur in initially sensitive isolates during prolong treatment(Gilad and Carmeli, 2008; Lesho *et al.,* 2013; Chen *et al*., 2015).

In a study conducted by Elham and Fawzia from 2015 to 2016, it was found that 8.5% of *Acinetobacter spp*. isolates were colistin-resistant and most of them (64%) were from seriously ill ICU patients (Elham and Fawzia, 2019).

This emphasizes the importance of colistin-resistant isolates among patients with *Acinetobacter spp.* bacteremia and Colistin therapy should be only initiated after antimicrobial sensitivity testing and depending on other clinical parameters.

CONCLUSION

Acinetobacter spp. are important organisms causing blood stream infections especially among critically ill patients in various ICUs. There is a male predominance. Patients of the older age group are the most vulnerable but the incidence is rising among paediatric and young adults. Most of the commonly used antibiotics like b-Lactams, Cephalosporins, and Fluroquinolones are becoming ineffective because of the high resistance among *Acinetobacter spp.* isolates. Carbapenems are currently the most preferred drug against such isolates but the resistance against Carbapenem antibiotics is on rising. Colistin resistance is still low among such isolates but drugs like colistin or carbapenems should only be used in MDR isolates detected by antimicrobial sensitivity testing and therapy should be initiated after analysing the patient's clinical parameters and risk profile.

Conflict of Interest- None

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Authors Contributions- Dr. Mukesh Azad Preparation of manuscript. Dr. Suprakash Das Collected and analyzed the data including statistical analysis. Dr. Asim Sarfraz assisted in drafting the manuscript and critical revision.

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