

## A RISING THREAT – RISK FACTORS AND OUTCOMES RELATED TO INFECTIONS WITH *ACINETOBACTER* SPECIES

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### ABSTRACT

**Objective:** *Acinetobacter* species is an important cause of community as well as nosocomial infections with a high mortality rate. The study was done to analyze the risk factors associated with *Acinetobacter* infections and their outcomes.

**Methods:** The clinical details of 100 patients having infections with *Acinetobacter* species over a period of 1-year were analyzed for underlying risk factors and outcomes. The antibiotic sensitivity results were interpreted according to the Clinical Laboratory Standards Institute guidelines.

**Results:** Majority of the infections caused by the *Acinetobacter* species were lower respiratory tract infections, most common being ventilator-associated pneumonia. 47% of the isolates were multi drug resistant and 26% were extensively drug resistant. There is a significant chance of drug resistance and a poor outcome with intensive care unit (ICU) stay, prolonged hospital stay of more than 7 days, the presence of 5 or more risk factors. Endotracheal intubation and mechanical ventilation were the risk factors for increased drug resistance in the ICU. Drug resistance was also seen more frequently in patients with chronic obstructive pulmonary disease, chronic kidney disease, and patients on post-operative care.

**Conclusion:** The steady increase in drug resistant *Acinetobacter* species and limited antibiotics available advocates an uncompromising approach toward infection control and a judicious use of antibiotics especially in the ICU. An understanding about the risk factors helps in the appropriate approach and management of the patient.

**Keywords:** *Acinetobacter*, Risk factors, Invasive procedures, Nosocomial.

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### INTRODUCTION

*Acinetobacter baumannii* has been notified by the Infectious Disease Society of America as “red alert” pathogen [1]. They are opportunistic pathogens and cause both community acquired and health-care associated infections such as nosocomial pneumonia, meningitis, urinary tract infection, skin and soft tissue infection and bacteremia, with a high mortality rate [2]. With the acquisition of antibiotic resistance genes, there is an increase in the prevalence of multi-drug resistance (MDR) in *Acinetobacter* species [3].

This study was done to analyze the factors responsible for infections caused by *Acinetobacter* species and those associated with infection due to MDR *Acinetobacter* strains.

### METHODS

This study is a prospective study conducted in intensive care units (ICUs) and wards of a tertiary care hospital in Mangalore, Karnataka, over a period of 1-year. 100 patients with infections caused by *Acinetobacter* species were analyzed for associated risk factors using the medical records of each patient. All outpatients and patients with colonization with *Acinetobacter* species were excluded from the study. Non-random sampling method was adopted for the study. The following variables were analyzed: ICU admission, duration of stay in the hospital, mechanical ventilation, endotracheal intubation, the presence of underlying diseases or conditions, including chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, chronic kidney disease (CKD), chronic liver disease, ischemic heart disease, malignancy, past history of device implantation or surgery, and instrumentation at various sites such as Central venous catheters [4-7]. Ventilator-associated pneumonia (VAP)

is defined according to the American Thoracic Society as pneumonia that occurs 48-72 hrs or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent [8].

The antibiotic susceptibility test results of these isolates of *Acinetobacter* species were interpreted according to Clinical Laboratory Standards Institute recommendations [9-11]. MDR *Acinetobacter* isolates were defined as non-susceptible to one or more agent in three or more antimicrobial categories. Extensively drug resistant (XDR) isolates were defined as non-susceptible to one or more agents in all but two or less antimicrobial categories, and pan-drug resistant (PDR) strains were defined as non-susceptible to all antimicrobial agents [12].

### RESULTS

Out of the total 100 patients included in the study, 63 were males and 37 were females. Maximum isolates (46 out of 100) were from the elderly population, i.e., >55 years of age, followed by 23 isolates in the age group 36-55 years, 16 isolates in the age group 16-35 years, 13 isolates in the neonates and 2 in children till 15 years of age.

The majority of the infections caused by *Acinetobacter* species occurred in patients admitted in the ICUs (73%). 61% of infections in our study were lower respiratory tract infections (LRTIs), out of which 54.1% (33 out of 61) were VAP. The specimen used were endotracheal tube secretions (35), sputum (21), and broncho alveolar lavage (5) (Table 1). To diagnose LRTI or VAP, strict diagnostic criteria was used and all colonizers were excluded from the study.

All the skin and soft tissue infections were post-operative cases where *Acinetobacter* species were isolated from the pus and wound swab specimens collected from the operated site.

About 72% of the infections caused by *Acinetobacter* species in the study were monomicrobial, while 28% were polymicrobial, most commonly associated with *Klebsiella* species (14%), followed by *Pseudomonas* species (5%), *Enterococcus* species (3%), *Staphylococcus aureus* (3%), *Citrobacter* species (2%), and *Candida* species (2%).

Risk factors associated with these infections caused by *Acinetobacter* species were analyzed. The most common risk factor for the development of infection with *Acinetobacter* species was intubation followed by mechanical ventilation and insertion of medical devices (Table 2). Diabetes was associated with 29 out of 100 patients.

Around 47% of these isolates were MDR while 26% of these isolates were XDR. There were no PDR strains.

67% of the patients suffering from the infections caused by *Acinetobacter* species improved, while 22% of the patients expired. 7% of the patients worsened while in 4%, the condition remained unchanged.

The majority of patients, i.e., 83% had a prolonged duration of hospital stay (7 days or more). Patients with prolonged ICU stay, i.e., more than 7 days had increased association with infections caused by MDR *Acinetobacter* species and also a poor outcome, i.e., worsening of the condition or mortality (p<0.05). There was significant chance of the *Acinetobacter* species being drug resistant when five or more risk factors were present (p<0.05). Mortality increased significantly when it was associated with one or more risk factors (p<0.001). When each of the risk factors was analyzed to risk of mortality and drug resistance, it was observed that only mechanical ventilation was significantly associated with both of them (p<0.05). But in the ICU settings, other risk factors such as endotracheal intubation, mechanical ventilation, post-operative case, COPD and CKD were also significantly associated with drug resistance (p<0.05).

**Table 1: Specimen wise isolation of *Acinetobacter* species**

Specimen	Number (n=100)
ET secretions	27
Sputum	21
Pus and wound swab	14
Blood	10
Oral suction catheter	08
CSF	5
Urine	5
BAL	5
Umbilical catheter tip	3
Central line tip	2

ET: Endotracheal tube, CSF: Cerebral spinal fluid, BAL: Broncho alveolar lavage

**Table 2: Risk factors associated with infection due to *Acinetobacter* species**

Risk factor	Number
Intubation	81
Mechanical ventilation	36
Instrumentation	35
Diabetes	29
Hypertension	26
Post-operative case	25
COPD	19
Ischemic heart disease	12
CKD	13
Chronic liver disease	5
Malignancy	7

COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease

**DISCUSSION**

*Acinetobacter* species, once considered to be a part of the commensal flora of humans, now pose a serious challenge, especially in health-care settings where it is now an important cause of life-threatening infections. The ability to survive for prolonged duration in the hospital settings and the rapid acquisition of MDR has made infections due to *Acinetobacter* species, a major concern in health-care settings.

We found increased incidence of infection in males (63%) and a male:female ratio of 1.7:1. LRTI due to *Acinetobacter* species was the most common infection in our study (61%). Most patients (63.9%) with LRTI belonged to the >55 years age group. 65.6% males had LRTI compared to only 34.4% of females which could be related to the increased history of smoking among men. Smoking damages the cilia in the respiratory tract and alters the structural and immune defenses of the host predisposing the host to infections. Advanced age is a risk factor for acquiring infection with *Acinetobacter* species which could be attributed to the poor immune defense mechanisms in the elderly age group and the presence of coexisting comorbidities and chronic diseases. Other studies on infections with *Acinetobacter* species also reported male preponderance and increased incidence in older group [6,13].

Nearly 35 (57.4%) of the isolates from LRTI were isolated from endotracheal tips and aspirates, 21 (34.4%) from sputum and 5 (8.2%) from bronchoalveolar lavage. 54.1% of these patients with LRTI had developed VAP. 14% of the infections were skin and soft tissue infections while 10% of the infections were blood stream infections. Similar results were obtained in the study done by Prashanth and Badrinath, in which they found respiratory tract infections to be the most common infection caused by *Acinetobacter* species (51.2%), followed by bloodstream infections (16.2%) [5]. In another study done by Lee et al., respiratory infections were the most common infections caused by both imipenem-resistant and imipenem-sensitive *A. baumannii* isolates, 57% and 64%, respectively [14]. The type of infections caused depends on the condition of the patients and the type of interventions and procedures performed, and thus varies from hospital to hospital. In our setup, 81% of the patients had endotracheal intubation and 36% of the patients were mechanically ventilated.

Mixed infections, combining *Acinetobacter* species along with other organisms have been found to be more virulent. These infections are more resistant to treatment and mortality is high in these patients like in studies by Telley and Roberts [15]. 28% of our patients had mixed infections. Most of these polymicrobial infections were from respiratory tract specimens (78.6%) and *Klebsiella pneumoniae* was the most common associated organism isolated from polymicrobial infections, followed by *Pseudomonas* species. In our study, 57.1% of the mixed infections were due to XDR *Acinetobacter* strains, 28.6% were due to MDR *Acinetobacter* strains. 53.6% of the mixed infections in our study were associated with mortality and poor outcome.

We found a strong association between ICU admission and development of infection with *Acinetobacter* species (p<0.05). The majority of the patients included in the study were admitted to the ICU (73%), which indicates that ICU admission is a predisposing factor for the occurrence of infections caused by *Acinetobacter* species. Similar results were found by Tripathi et al. [16], Lone et al. [6] who found that *Acinetobacter* infections in the ICU were significantly more common than those in the general ward. Patients in ICU are sicker and require more invasive monitoring and therapeutic procedures. The environmental contamination of the ICU and transmission of the infection from colonized patients is probably another important source of infection due to *Acinetobacter* species. The development of ICU-acquired infections is associated with worse outcomes including increased morbidity and mortality [17]. 75.3% (55 out of 73) of the patients admitted to the ICU were infected with drug-resistant strains of *Acinetobacter* species, 54.8% of the strains being XDR and 20.5% of the strains being MDR. The increased drug resistance seen in the ICU

settings is probably because of the extensive use of broad-spectrum antibiotics for the critically ill patients. The mortality in the ICU settings was 30.14%. All the 22 patients who expired were admitted in the ICU.

Risk factors like prolonged duration of stay in the hospital, intubation, mechanical ventilation, post-operative cases, and chronic underlying conditions such as diabetes mellitus, hypertension, ischemic heart disease, COPD, chronic liver disease, CKD, and malignancy were analyzed. Among these, intubation was the most common underlying predisposing factor present in 81% of the patients. Among the patients suffering from respiratory tract infections with *Acinetobacter* species, 86.9% were intubated during the course of the admission. All the 14 patients suffering from skin and soft tissue infections due to *Acinetobacter* species, were post-operative cases and the specimen was taken from the site of operation. Among the 5 patients suffering from urinary tract infection due to *Acinetobacter* species, 4 patients had urinary catheters inserted. Studies, conducted by Tripathi *et al.* [16] and Lone *et al.* [6] found that mechanical ventilation, admission to ICU, underlying chronic debilitating condition and a prolonged hospital stay were significant predisposing factors. The increased occurrence of infection by *Acinetobacter* species in patients with underlying chronic conditions reiterates the important opportunistic characteristic of *Acinetobacter* species, which affects compromised hosts. Prolonged hospital stay of more than a week also predisposes the patient to the hospital environment and stresses on the nosocomial character of the organism. 83% of the patients in our study had a prolonged hospital stay of more than a week. *Acinetobacter* strains have the ability to adhere to the surfaces by forming biofilm [18]. This is probably the reason why intubation and instrumentation like catheterization expose the person to infections caused by *Acinetobacter* species.

The occurrence of bacteremia due to *Acinetobacter* species in our study was 10%. Out of the 10 patients, 3 were secondary to an indwelling catheter, 2 were secondary to VAP, and 2 were secondary to a urinary tract infection, while in 3 patients, the source was unknown. Prashanth *et al.* in their study found the incidence of bacteremia to be 16.27% with the most common source being respiratory tract infection (65%) [5]. Intravascular catheters and respiratory tract infections are the most common sources of bacteremia by *Acinetobacter* species, while urinary tract infections and surgical wounds are the less common sources. These stress the importance of indwelling catheter care and infection control policies in preventing bloodstream infections due to *Acinetobacter* species. Some of the bacteremia's with source unknown could be secondary to undiagnosed vascular catheter infections or have an intestinal origin due to bacterial translocation. This is supported by the demonstration that digestive tract colonization by *A. baumannii* is more frequent and advanced in ICU patients [19,20].

In our study, the mortality due to infection caused by *Acinetobacter* species was 22%. The presence of risk factors in our study was statistically significant to mortality. Mechanical ventilation significantly increased the chances of mortality. Earlier studies reported a mortality rate of 23% in their study, with mechanical ventilation and infection with drug-resistant isolates as the risk factors associated with mortality [5]. Ventilator-associated pneumonia due to non-fermenting Gram-negative bacteria like *Acinetobacter* species is a known cause of increased mortality in hospitals [21]. Mortality and poor clinical outcomes are also due to high incidence of drug resistance in *Acinetobacter* species. This leaves the clinician with few treatment options and also the empiric therapy given is not effective.

Individually, among all the risk factors, mechanical ventilation was significantly associated with increase in drug resistance of the isolate. Furthermore, the presence of five or more risk factors is significantly associated with increase in drug resistance. Fukuta *et al.* and Surasarang *et al.* in their individual studies found mechanical ventilation, prolonged intensive unit care stay and prior antimicrobial use to be significant risk factors for acquisition of infection due to MDR *Acinetobacter* isolates [22,23]. Pertaining solely to the ICU settings,

the risk factors that significantly lead to increase in drug resistance were found out to be mechanical ventilation, endotracheal intubation, post-operative cases and COPD and CKD. In addition to more severe health conditions of patients in ICU settings, cross-contamination, to a large extent, is associated with the high drug resistant rate, which has been demonstrated by numerous outbreaks of MDR isolates in critical centers [24,25]. Accordingly, to avoid the transmission of environmental organisms to patients from contaminated hands of medical staff and equipment, it is of great necessity and importance to reinforce the infection control strategies like hand washing and bundle care, especially in the ICU setting.

The *Acinetobacter* isolates causing infection in the ICU settings were significantly more resistant to antibiotics as compared to the isolates causing infection in the Ward settings ( $p < 0.05$ ). In our study, 57% of the *Acinetobacter* isolates which caused infection were carbapenem-resistant. Intra-hospital and inter-hospital spread of MDR *Acinetobacter* species, especially carbapenem-resistant *A. baumannii* is becoming an issue of concern and leads to further spread of drug-resistant *Acinetobacter* strains, leaving no option apart from polymyxins for treatment [26]. Because of the same reasons, mortality was also found out to be significantly high in patients with infection with drug resistant *Acinetobacter* strains rather than susceptible *Acinetobacter* strains ( $p < 0.05$ ).

## CONCLUSION

*Acinetobacter* species, especially *A. baumannii* is an important cause of severe nosocomial infections and hospital outbreaks; hence, this study of *Acinetobacter* species and their antibiotic susceptibility pattern is of immense significance. Although the resistance rates for these pathogens have been increasing steadily, the development of new drugs for these infections has not increased proportionately. Infections due to MDR *Acinetobacter* species increase the cost of treatment and severely affects clinical outcome and has very limited treatment options which include polymyxins. The present scenario of escalating drug resistance in *Acinetobacter* species highlights the importance of uncompromising approach towards infection control, especially in the ICUs. An attempt to study the risk factors and the conditions that predispose a person to infections due to *Acinetobacter* species will help the treating physician to approach a patient and manage the infection along with the underlying condition appropriately.

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