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# CARBAPENEM RESISTANT ACINETOBACTER BAUMANNII - A CHALLENGING THREAT IN HEALTHCARE

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## ABSTRACT

**Introduction:** Carbapenem resistant *Acinetobacter baumannii* (CRAB) has emerged worldwide, as an alarming pathogen causing healthcare associated infections. It mostly involves patients with impaired host defenses, and those with debilitating illnesses. CRAB is declared as the top priority pathogen by the World Health Organization for the development of new drugs. **Aims & Objectives:** i) To determine the frequency of isolation of *Acinetobacter baumannii* from clinical samples ii) To detect carbapenem resistance in clinical isolates of *A. baumannii* iii) To understand the risks factors associated with acquisition of CRAB. **Methods:** The clinical samples were subjected to culture i) by conventional methods as per standard bacteriological techniques, and ii) by an automated BACTEC System (BD). The isolates grown onto culture media were identified i) by conventional methods, and ii) by an automated VITEK 2 system (Biomerieux). Antibiotic susceptibility testing was performed i) by the Kirby Bauer disc diffusion method as per CLSI guidelines, and ii) by VITEK 2 system. All the meropenem resistant isolates of *A. baumanni* were subjected to i) Modified Hodge Test (MHT) for the production of carbapenemase, and ii) Combined Disk Test (CDT), using imipenem and EDTA, for the production of metallo-beta-lactamase. **Results:** The frequency of isolation of *Acinetobacter* species was found to be 5.7%, of which the predominant was *A. baumanni* (89.3%). Among the isolates of *A. baumannii*, the frequency of meropenem resistance was found to be 72.1%. Meropenem resistant isolates of *A. baumannii* were most commonly obtained from patients admitted in intensive care units (86.3%). CRAB isolates were most frequently recovered from endotracheal aspirate (34.2%), followed by pus (29.8%), blood (20.7%), sputum (8.2%) and urine (5.6%) The most common risk factor associated with CRAB was mechanical ventilation (35.5%), followed by previous antibiotic usage (28.5%), indwelling catheters (11.1%), prolonged hospitalization (9.7%), chronic obstructive pulmonary disease (8.1%) and diabetes (5.7%). Out of 922 CRAB isolates, 757 (82.1%) were carbapenemase producers. Among the CRAB isolates, 31.9% were found to be only MHT positive, 26.7% were only CDT positive, 23.5% were both MHT and CDT positive, and the remaining 17.9% were both MHT and CDT negative. **Conclusion:** Emergence of infections with CRAB emphasizes the need for continuous surveillance, judicious use of antibiotics, and implementation of aggressive infection control strategies.

**KEYWORDS :** Acinetobacter baumannii, carbapenem resistance, CRAB, carbapenemase, MBL

## INTRODUCTION:

The genus *Acinetobacter* comprises of aerobic, cytochrome oxidase-negative, non-motile, non-pigmented, Gram-negative coccobacilli[1,2] *Acinetobacter* was first isolated by a Dutch microbiologist, Beijerinck, in 1911, but was not definitively recognized until 1971.[3] Although there are more than 50 species within the diverse *Acinetobacter* genus, the majority are innocuous environmental species, most commonly found in soil and water.[1,2,4] In 1986, Bouvet and Grimont, distinguished 12 genospecies within the genus on the basis of DNA–DNA hybridization, some of them were given formal species names, including *A. baumannii*, *A. calcoaceticus*, *A. haemolyticus*, *A. johnsonii*, *A. junii*, and *A. lwoffii*.[5] Among the *Acinetobacter* species, *A. calcoaceticus*, *A. baumannii*, *Acinetobacter* genomic species 3 and *Acinetobacter* genomic species 13TU share close relationship and are difficult to distinguish from each other by phenotypic tests alone. Hence, they have been grouped as the *A. calcoaceticus-A. baumannii* complex.[1,6]

The species of special concern is *Acinetobacter baumannii*, due to its notable role in colonization and infection in hospitalized patients. Its ability to survive in the hospital environment and its dexterity to persist for prolonged periods on surfaces makes it a common cause of healthcare associated infections.[7,8] The increased risk of infection with *A. baumannii* in a healthcare setting is often associated with the severity of patient's illness, prolonged hospitalization, and length of exposure to invasive devices and procedures.[9] Infections caused by *A. baumannii* include pneumonia, meningitis, bloodstream, urinary tract infection, and surgical site infections.[1,10] *A. baumannii* has the ability to accumulate diverse mechanisms of resistance, leading to the appearance of strains that are resistant to most available antibiotics.[11] Of serious concern is the carbapenem resistant *Acinetobacter baumannii* (CRAB), which has emerged globally, threatening the human health and healthcare systems. A complex interaction of multiple mechanisms of carbapenem resistance in *A. baumannii* includes the production of carbapenemases (class D enzymes or oxacillinases and class B enzymes or metallo-beta-lactamase), alterations in penicillin-binding proteins, loss of outer membrance porins and overexpression of efflux pumps.[12,13] WHO has classified CRAB amongst the critical priority pathogens in the global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.[14] The challenges in treating CRAB infections stem from a formidable antimicrobial resistance profile, leaving behind only a few therapeutic options of uncertain efficacy, such as colistin and tigecycline.[15]

## MATERIALS AND METHOD:

The prospective study was conducted in a tertiary care hospital in western Uttar Pradesh, for the period of 2 years (from May 2021- April 2023). The study group included all the clinical samples received for bacterial culture and sensitivity, in the Microbiology laboratory, from various in-patient and out-patient departments. Approval from the institutional ethics committee was taken before carrying out the study.

### Sample Processing:[1,2]

Clinical samples were subjected to culture i) by conventional methods as per standard bacteriological techniques,[1,2] and ii) by an automated BACTEC System (BD) as per the manufacturer's instructions. The isolates grown onto culture media were identified i) by conventional methods such as colony characteristics, culture smears, motility and

biochemical tests,[1,2] and ii) by an automated VITEK 2 system (Biomerieux), using VITEK 2 GN REF 21341 card. Genus *Acinetobacter* was identified conventionally as Gram-negative coccobacilli, non-motile, catalase-positive, oxidase-negative, nonfermenter and nitrate reduction test negative. *Acinetobacter* was speciated as *A. baumanni* on the basis of oxidative pattern in Hugh and Leifson's oxidation-fermentation (OF) glucose, growth at 42°C, and positive arginine dihydrolase test.[1,2] Antibiotic susceptibility testing was performed i) by Kirby Bauer disc diffusion method as per CLSI guidelines[16], and ii) by VITEK 2 AST-N 281 REF414532 card.

**Screening of carbapenem resistance:**

Isolates of *A. baumanni* were screened for carbapenem resistance using meropenem disc (10μg), by Kirby Bauer disc diffusion method.[16]

**Detection of carbapenemase production:**

All the meropenem resistant isolates of *A. baumanni* were subjected to Modified Hodge Test (MHT) for the production of carbapenemase.[16] MHT was performed using meropenem disc (10μg) and *Escherichia coli* ATCC 25922. The test was considered positive by the presence of a clover leaf like indentation of standard strain of *E. coli* growing along the test organism growth streak within the disc diffusion zone.[16]

**Detection of metallo-beta-lactamase (MBL) production:**

All the meropenem resistant isolates were subjected to Combined Disc Test (CDT) for the production of MBL.[16] CDT was carried out using imipenem and ethylene diamine tetra acetic acid (EDTA). An increase in zone diameter of ≥7 mm around the imipenem-EDTA disc as compared to the zone diameter around imipenem disc alone was considered positive for MBL.[16]

## RESULTS:

A total of 25279 samples were received for bacterial culture and sensitivity, out of which 1432 (5.7%) were found to be culture positive for *Acinetobacter* species. Among the *Acinetobacter* isolates obtained, 89.3% (1279/1432) were of *Acinetobacter baumannii* and the remaining 10.7% (153/1432) were of *Acinetobacter lwoffii*. *A. baumannii* being the most predominant species isolated (n=1279), was most frequently recovered from endotracheal aspirate (28.9%), followed by blood (24.4%), pus (21.7%), sputum (14.3%), urine (5.8%), broncho-alveolar lavage (3.8%), pleural fluid (0.5%), ascitic fluid (0.3%), menstrual fluid (0.2%) and synovial fluid (0.1%). *A. baumannii* was isolated mainly from intensive care units (631/1279, 49.3%), followed by wards (362/1279, 28.3%) and out-patient departments (286/1279, 22.4%) (Figure-1). On analyzing the antibiogram, among the isolates of *Acinetobacter* (n=1432), 67.9% (972/1432) were resistant to meropenem, out of which majority were *A. baumannii* (922/972, 94.9%). Thus, among the isolates of *A. baumannii*, the frequency of meropenem resistance was found to be 72.1% (922/1279).

Meropenem resistant isolates of *A. baumannii* were most commonly obtained from patients admitted in ICUs (796/922, 86.3%). CRAB isolates were most frequently recovered from endotracheal aspirate (34.2%), followed by pus (29.8%), blood (20.7%), sputum (8.2%), urine (5.6%), broncho-alveolar lavage (1.2%) and pleural fluid (0.2%) (Table-1). The most common risk factor associated with CRAB was mechanical ventilation (35.5%), followed by previous antibiotic usage (28.5%), indwelling catheters (11.1%), prolonged hospitalization (9.7%), chronic obstructive pulmonary disease (8.1%), diabetes (5.7%), surgical procedures (0.9%) and neurological impairment (0.5%) (Table-2). Out of 922 CRAB isolates, 757 (82.1%) were found to be carbapenemase producers. Looking at the phenotypic characterization of CRAB (n=922), 294 isolates (31.9%) were found to be only MHT positive, 246 (26.7%) isolates were only CDT positive, 217 (23.5%) were both MHT and CDT positive, and the remaining 165 (17.9%) were both MHT and CDT negative (Table-3).

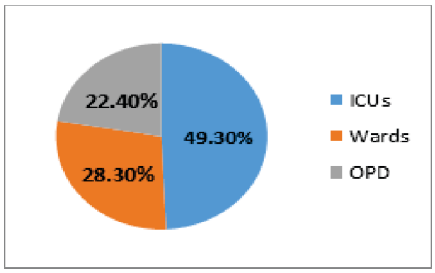


**Figure-1: Distribution of isolates of *Acinetobacter baumannii* (n=1279) from wards, ICUs, OPD:**

**Table-1: Frequency of isolation of meropenem resistant *A. baumannii* (n=922) from various clinical samples:**

| Clinical samples | Number of isolates (n=922) | Percentage % |
|---|---|---|
| Endotracheal Aspirate | 315 | 34.2% |
| Pus | 275 | 29.8% |
| Blood | 191 | 20.7% |
| Sputum | 76 | 8.2% |
| Urine | 52 | 5.6% |
| Broncho-alveolar lavage | 11 | 1.2% |
| Pleural fluid | 2 | 0.2% |

**Table-2: Risk factors associated with acquisition of CRAB (n=922):**

| Clinical samples | Number (n=922) | Percentage % |
|---|---|---|
| Mechanical ventilation | 327 | 35.5% |
| Previous antibiotic use | 263 | 28.5% |
| Indwelling lines and catheters | 102 | 11.1% |
| Prolonged hospital stay ( ≥7 days) | 89 | 9.7% |
| Chronic Obstructive Pulmonary Disease | 75 | 8.1% |
| Diabetes | 53 | 5.7% |
| Surgical procedures | 8 | 0.9% |
| Neurologic impairment | 5 | 0.5% |

**Table 3: Phenotypic characterization of meropenem resistant isolates of *A. baumannii* (n=922):**

| Total number of meropenem resistant isolates of A. baumannii (n=922) | Only MHT Positive | | Only CDT Positive | | Both MHT & CDT Positive | | Both MHT & CDT Negative | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| | 294 | 31.9 | 246 | 26.7 | 217 | 23.5 | 165 | 17.9 |

## DISCUSSION :

*Acinetobacter baumannii* has emerged as a precarious hospital pathogen by its ability to remain resilient against traditional disinfection measures and by exhibiting high levels of resistance to antibiotics.[17] Due to its proclivity for multidrug-resistance, *A. baumannii* has become as a big health concern. The most troublesome is an increase of carbapenem resistance in *A. baumannii*.[18,19] The burden of CRAB represents a therapeutic threat. The antimicrobial choices for CRAB are limited and have pharmacokinetic limitations, such as high toxicity and low plasma levels.[15] In these atrocious circumstances, the need for newer drugs for the treatment of CRAB infections is incontestable.

In our present study, the frequency of isolation of *Acinetobacter* species was found to be 5.7%. Similar observations have been made in a study done by Rit et al. in West Bengal[20] and in a study by Vashishtha A et al. in western Uttar Pradesh[21], who had reported the isolation rate of

*Acinetobacter* species as 4.5% and 4.16%, respectively. *Acinetobacter* prevalence of 3% has been documented in Odisha by Dash et al.[22] The studies done in Pune by Gupta et al.[23] and by Joshi et al.[24] had reported *Acinetobacter* isolation of 3.36% and 9.6%, respectively. Prevalence of 2.9% *Acinetobacter* species was found by Saha S et al.[25] in Manipur. Wajid M et al.[26] had documented the isolation rate of *Acinetobacter* species as 7.24 % in Hyderabad.

In our study, we found that among the *Acinetobacter* isolates obtained from various clinical samples, 89.3% (1279/1432) were of *A. baumannii* and the remaining 10.7% (153/1432) were of *A. lwoffii*. Our observation of higher frequency of isolation of *A. baumannii* was consistent with the study conducted in 2021 in Amritsar by Kaur R et al.[27] who has reported that among the *Acinetobacter* isolates, 91.6% were of *A. baumanii*, followed by *A. lwoffi* (5.6%) and *A. hemolyticus* (2.8%). Saha S et al.[25] found that 98.2% isolates were *A. baumannii* whereas remaining 1.8% were *A. lwoffii*. Dash M et al.[22] observed that *A. baumannii* was the predominant species responsible for 79.6% of the infections, followed by *A. lwoffii* (12.4%), and other *Acinetobacter* species (8%). In 2013, Sinha N et al.[28] reported that *A. baumannii* was the predominant species (92.14%) isolated, while *A. lwoffii* and *A. haemolyticus* accounted to be 6.42% and 1.42%, respectively.

In our set up, *A. baumannii* was most frequently isolated from endotracheal aspirate (28.9%), followed by blood (24.4%), pus (21.7%), sputum (14.3%), urine (5.8%) and broncho-alveolar lavage (3.8%). In 2021, Wajid M et al.[26] had also reported maximum isolation from endotracheal secretions, followed by blood and pus. Rekha et al.[29] also observed higher isolation rate from respiratory samples in Kolar. However, these findings were not in agreement with the studies done by Saha S et al.[25] and Kaur R et al.[27] who had reported higher isolation from urine, whereas Sinha N et al.[28] and Murugesh K et al.[30] reported significant isolation from pus and blood.

It has been observed that *A. baumannii* is found predominantly in ICUs, affecting debilitated patients with compromised barrier integrity and / or disruption of normal flora. *A. baumannii* is considered as a serious menace in hospital settings, particularly when it infects the critically ill patients.[14,19]

In our study, isolates of *A. baumannii* were recovered mainly from ICUs (49.3%), followed by wards (28.3%) and out-patient departments (22.4%) (Figure-1). Dash et al.[22] and Sinha N et al.[28] had also reported maximum isolation from ICUs, whereas Kaur R et al.[27] and Murugesh K et al.[30] observed that the majority of these isolates were recovered from wards. This variation could be due to the varying prevalence rates of *Acinetobacter* in different healthcare facilities and geographical areas. The emergence of *A. baumannii* as the causative agent of nosocomial infections in ICUs is probably related to the prolonged duration of stay, over usage of broad spectrum antibiotics, invasive interventions such as use of mechanical ventilation or catheters, and invasive diagnostic procedures.[29]

Carbapenem is an important therapy for serious healthcare-associated infections caused by multidrug-resistant organisms, specifically *A. baumannii*. The global increase of CRAB infections has significantly threatened public health.[24] *A. baumannii* is accredited as one of the six intricate pathogens "ESKAPE" (*Enterococcus faecium, Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa* and *Enterobacter* species) that exhibit multidrug resistance.[29] *A. baumannii* is endowed with an inherent carbapenem- hydrolysing oxacillinase OXA-51 that confers resistance to carbapenems only when over-expressed. The most common mechanism of acquired resistance to carbapenem in *A. baumannii* is the production of oxacillinase OXA-23 like, OXA 24/40-like, OXA-58 like, OXA-143 like or OXA-235 like.[11] Carbapenemase encoding genes can be carried within *A. baumannii* genome on chromosomes and / or plasmids, while acquisition of new resistance mechanisms can be mediated by mobile genetic elements such as transposons, insertion sequences, integrons and resistance islands.[31]

In our present study, among the isolates of *A. baumannii*, the frequency of CRAB was found to be 72.1%, which corroborates with the studies done by Shareek et al.[32] and De Francesco MA et al.[33] that had reported carbapenem resistance as 75% and 80%, respectively. In comparison to our data, lower rates of carbapenem resistance has been reported by other studies.[22,25,27,30] In a study done by Wajid M et al.[26], carbapenem resistance was found to be 55.6%. Dash et al.[22] had reported resistance towards meropenem as 22% and towards imipenem as 19%. Saha S et al.[25] observed resistance towards imipenem and meropenem to be 25.3% and 29.7%, respectively. A study done by Kaur R et al.[27] found resistance towards meropenem and imipenem as 55.6% and 49.4%, respectively.

In our present study, CRAB isolates were most commonly obtained from patients admitted in ICUs. We observed that the isolates of CRAB were most frequently recovered from endotracheal aspirate (34.2%), followed by pus (29.8%), blood (20.7%), sputum (8.2%) and urine (5.6%) (Table-1). The emergence of antibiotic resistant strains in ICU is attributed to the escalation in the usage of antimicrobial agents per patient and per surface area.[23] In 2016, a study done in Bathinda by Kaur A et al.[34] found that *A. baumannii* was resistant to all routinely used antibiotics in ICU patients, and these isolates were predominantly recovered from respiratory samples. Saha S et al.[25] and Wajid M et al.[26] also obtained majority of the drug resistant isolates from ICU patients.

In our setup, the most common risk factor associated with CRAB was found to be mechanical ventilation (35.5%), followed by previous antibiotic usage (28.5%), indwelling catheters (11.1%), prolonged hospitalization (9.7%), chronic obstructive pulmonary disease (8.1%) and diabetes (5.7%) (Table-2). Case-control studies have shown that prior exposure to antibiotic therapy has been the commonest risk factor identified in multivariate analysis. Carbapenems and third-generation cephalosporins are the most commonly implicated antibiotics. The second most common risk factor identified in case-control studies is mechanical ventilation.[10,35]

In our study, out of 922 CRAB isolates, 757 (82.1%) were found to be carbapenemase producers. Among the CRAB isolates, 31.9% were found to be only MHT positive, 26.7% were only CDT positive, 23.5% were both MHT and CDT positive, and the remaining 17.9% were both MHT and CDT negative (Table-3). Thus, we observed that MHT could detect carbapenamase production in more number of isolates in comparison to CDT. Our study also reflects that 23.5% (both MHT and CDT positive) of CRAB isolates showed the production of serine carbapenemases and MBLs. However, the isolates which were both MHT and CDT negative (17.9%) could be due to other causes of carbapenem resistance like porin loss.

Vashishtha A et al.[21] found that among the meropenem-resistant isolates of *A. baumannii*, 39.21% were only MHT positive, 50.98% were only CDT positive, and 17.64% were both MHT and CDT positive. Sinha N et al.[28] detected that 57.14% isolates of meropenem-resistant *A. baumannii* were MBL producers.

Colistin (polymyxin E) and tigecycline are the alternatives in the treatment of CRAB infections.[22] In our set up, all the CRAB

isolates were found to be susceptible to colistin and tigecycline, which is similar to the trend observed in various studies.[22,25,27,32] However, a study done in Chandigarh by Taneja et al. reported resistance to both colistin and tigecycline in 3.5% isolates of *A. baumannii*.[36]

## CONCLUSION:

Carbapenem resistant *Acinetobacter baumannii* (CRAB) is a global health concern as a cause of serious nosocomial infections. The occurrence of serine carbapenemase producing *A. baumannii* and metallo-beta-lactamase producing *A. baumannii* poses a therapeutic confrontation, leaving behind very limited treatment choices. Our study stress upon the necessity to impose strict infection control strategies and perpetual antimicrobial stewardship programs to thwart the spread of multidrug resistant bugs and to prevent microbial resistance catastrophe.

### Limitations:

Definitive identification and characterization of serine carbapenemases and metallo-beta-lactamases by molecular techniques could not be done due to resource constraints.

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