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REVIEW ARTICLE

Multidrug Resistant *Acinetobacter* in Patient with Ventilator Associated Pneumonia: Review Article

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Abstract:

Acinetobacter is a complex genus, with multiple species. *Acinetobacter* species are the common etiology of nosocomial infections, principally nosocomial pneumonia catheter-associated bacteremia and urinary tract infections. Multidrug Resistant (MDR) Ventilator Associated Pneumonia (VAP) by *Acinetobacter* spp is increasingly reported from different parts of the world. Transmission of *Acinetobacter* is aid by the organism's environmental stubbornness, resistance to desiccation and evasion of host immunity. The virulence properties demonstrated by *Acinetobacter* spp. is primarily by evasion of rapid clearance by the immune system. The capsular polysaccharide is a critical virulence factor that enables immune evasion and lipopolysaccharide triggers septic shock. Conversely, the primary factor of clinical outcome is antibiotic resistance. *Acinetobacter* spp. has become a discreditable threat for patients on mechanical ventilation. Considering high rate of antibiotic resistance, new preventive and therapeutic alternative approach for MDR *Acinetobacter* spp. infections are urgently needed. Worldwide drug resistance in *Acinetobacter baumannii* is growing. This review article is emphasised on incidence of VAP due to MDR *Acinetobacter*, phenotypes, genotypes, associated risk factors and preventive strategy.

Keywords: *Acinetobacter* spp, Ventilator Associated Pneumonia, Mechanical Ventilation, Multidrug Resistant, Phenotypes, Genotypes

Introduction:

The species *Acinetobacter baumannii* (*A. baumannii*) was largely unknown 30 years ago. *Acinetobacter species* (spp) are Gram-negative bacteria that have become one of the most difficult pathogens to treat. It is now a predominant pathogen in many hospitals as it has acquired resistance genes to virtually all antibiotics capable of treating Gram negative bacteria, including the fluoroquinolones and the cephalosporins. Over a decade, nosocomial infections due to *A. baumannii* have increased towards Multidrug Resistance (MDR), mostly in intensive care units with patients on ventilator. *A. baumannii* is a rapidly emerging nosocomial pathogen and causes severe infections that include bacteraemia, pneumonia, meningitis, urinary tract and wound infections. It has now become a major cause of nosocomial infection worldwide due to its notable inclination to swiftly acquire resistance to a wide range of antibacterial agents [1]. Ventilator-associated Pneumonia (VAP) is one of the most common Intensive Care Unit (ICU) acquired infection (6 to 52%) and a major cause of morbidity, mortality and increased financial load in ICUs. The overall rate of VAP is higher in developing countries (13.6) ICUs than quoted from the US (3.3 per 1000 ventilator-days). Despite of low virulence, *A. baumannii* has emerged as MDR pathogen responsible for hospital acquired infections that are difficult to control and treat. *A. baumannii* has natural MDR phenotype, its capability of acquiring new

mechanisms of resistance. Recently genome sequencing of several *A. baumannii* isolates, has led to the discovery of the extraordinary plasticity of their genomes, which is linked to their great proclivity to adapt to any environment [2]. In India, VAP caused by MDR-*Acinetobacter baumannii* (MDR-AB) isolates are associated with significant mortality, morbidity and costs. MDR-AB infections are difficult to treat owing to the extremely limited treatment options [3, 4]. Current knowledge about *A. baumannii*, including phenotypes, genotype, epidemiological aspects and resistance to antibiotics, are reviewed in this article. The present review reports the incidence of VAP, incidence of MDR VAP due to *A. baumannii*, risk factors for developing MDR-VAP due to *A. baumannii* and preventive strategy for MDR in the different parts of world have been discussed.

Rationale of review:

Multidrug resistant among *Acinetobacter* infection is associated with a high mortality rate and limits the therapeutic options. During the past few decades, *Acinetobacter* has emerged as an important nosocomial pathogen, affecting patients in the ICU setting, globally. *A. baumannii* has been recognised as a leading cause of VAP in various parts of the world. VAP remain important causes of morbidity, mortality and financial burden. Increasing antimicrobial resistance has stir up the concern of the failure of antibiotic treatment. VAP due to MDR *Acinetobacter* has different phenotypes, genotypes, antibiotic resistance pattern and associated risk factors for developing VAP, across the world. We performed a review of MDR-VAP due to *A. baumannii.*

Database searches and study selection:

Studies included in this review are, cross-sectional, case-control, cohort studies and systemic review. The relevant studies were identified from searches of the PubMed, Medline, Embase and Scopus databases (using keywords: *A. baumannii,* MDR-Ventilator associated pneumonia, phenotype, and genotype of MDR - *A. baumannii*). All studies included in this review were monitored for the development of VAP using clinical and microbiological criteria, until discharge or death.

The diagnosis of VAP was established on the basis of clinical and radiological parameters as per Centre of Disease Centres (CDC) Guidelines [5].

Diagnostic criteria and case definition for VAP:

VAP is defined as a pneumonia occurring 48 h or more after endotracheal intubation, with new and/or progressive radiological infiltrate, and at least two of the following features:

A. Radiology:

Two or more serial chest radiographs with at least one of the following:

New or progressive and persistent infiltrate consolidation, cavitations

B. Signs, symptoms and laboratory

For any patient, at least one of the following:

- Fever (>38°C or >100.4°F) with no other recognized cause
- Leucopoenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3)
- For adults >70 years old, altered mental status with no other recognized cause and at least two of the following
    1. New onset of purulent sputum or change in character of sputum or increased respiratory secretions, or increased suctioning requirements
    2. New onset or worsening cough or dyspnoea or tachypnea

3. Rales or bronchial breath sounds
4. Worsening gas exchange PaO_2/FiO_2 <240 (increased oxygen requirements or increased ventilator demand

- **The Clinical Pulmonary Infection Score (CIP):**
  (CPIS) is based on six clinical assessments, for patients clinically suspected of VAP on the day of endotracheal secretions collection, (CPIS with score ⩾6).
  Positive quantitative culture of the EA (count ⩾106 CFU/mL)
  MDR pathogens were defined as resistant to three or more classes of antibiotics.
- **Early-onset VAP:**
  Patients developing VAP within the first four days of Mechanical Ventilation (MV) were classified as having early onset VAP
- **Late-onset VAP:**
  Patients developing VAP five or more days after the initiation of MV were classified as having late onset VAP

Microbiological methods:

Susceptibility to different classes of antibiotics was determined by the Kirby Bauer disc diffusion method and interpreted. [Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing] Phenotypic and genotypic resistance to β-lactamases was determined using standard methods [6]. Combination disk method, modified Hodge test, EDTA disk synergy test and AmpC disk test were performed for detection of Extended Spectrum β-lactamases (ESBL), carbapenemases, Metallo-β-lactamases (MBL) and AmpC β-lactamases respectively in various studies. *bla*OXA-23, *bla*OXA-24, *bla*OXA-58, *bla*OXA-51, *bla*TEM, *bla*SHV, *bla*CTX-M, and *bla*PER β-lactamase genes were searched by Polymerase Chain Reaction (PCR) and sequencing. Pulsed-field gel electrophoresis for genotyping and antimicrobial susceptibility testing for clinically relevant antimicrobials were performed in these studies [7]. Resistance determinants were characterized by using different phenotypic (accumulation assay for efflux) and genotypic (PCR, DNA sequencing, plasmid analysis and electroporation) analysed by various studies according to protocol.

Characteristics of *Acinetobacter* spp:

Gram-negative coccobacilli that were likely *Acinetobacter* were isolated as early as 1914 and repeatedly through the 1940s but were previously referred to as Mimapolymorphia (now *Acinetobacter lwoffii*), Herelleavaginicola (now *A. baumannii* or *A. calcoaceticus*), Bacterium anitratum, B5W, and *Moraxella lwoffii* [1]. *A. baumannii* is a ubiquitous, non-fermenting, aerobic Gram-negative bacterium with intrinsic resistance to multiple antimicrobial drugs [2]. The genus, *Acinetobacter*, as has been currently defined, comprises Gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive, oxidase-negative, coccobacilli and opportunistic bacteria. *A. baumannii* is an encapsulated containing proteins, namely porins and efflux channels, on the outer cell membrane, which mainly contribute to their resistance mechanisms. This genus has undergone significant taxonomic modifications over the last 30 years. Compared to other Gram negative bacteria, it has fewer and smaller porin channels, which thereby decrease its cell permeability and increase its antibiotic resistance. The cell wall of the bacteria changes according to the environmental

conditions, thus causing an increase in its thickness when it is placed in a very dry conditions, thereby again providing extra resistance at high temperatures and dormant conditions. *A. baumannii* is generally considered as opportunistic infections and can be non-pathogenic in healthy individuals [8]. *A. baumannii* is one of the most important nosocomial pathogens because of its longevity in the hospital environment and ability to resist various antimicrobial agents and to colonize susceptible patients treated with broad-spectrum antibiotic [9].

Biology, virulence factors, risk factors for Drug resistance in *Acinetobacter* spp:

Acinetobacter was described by a Dutch microbiologist a century ago, as *Micrococcus calcoaceticus* known as *Acinetobacter* in 1950's and more than 25 species have been identified. Most of the cases are usually seen in the ICUs of hospitals, in patients with deprived immunity and in those who are on various invasive equipments, like ventilator machines and catheters. The irrational use of antibiotics in the ICU set up and the various bacterial mechanisms of resistance contribute to summation of resistance function for this untreatable, risky microorganism. Risk factors for colonization or infection with multidrug-resistant *A. baumannii* are prolonged length of hospital stay, exposure to an ICU, mechanical ventilation, prolonged exposure to antimicrobial agents, surgical and invasive procedures, and severe illnesses or comorbidites. Presence of the porin channels, efflux mechanisms and the non static behaviour of the bacteria in hot and humid conditions lead to extensive antimicrobial resistance. There is rising concern about antimicrobial resistance among *Acinetobacter* spp since the past decade [10].

The virulence factor like Porin (OmpA, Omp33-36, Omp22, CarO, OprD-like) are involved in adherence and invasion, induction of apoptosis, serum resistance, biofilm formation. Capsular Polysaccharides are required for growth in serum, survival in tissue infection, biofilm formation. Capsular Lipopolysaccharides (LPS) and Phospholipase (PLC and PLD) are responsible for Growth in serum, survival in tissue infection, biofilm formation, serum resistance, invasion, *in vivo* survival. Outer Membrane Vesicle (OMV) is involved in delivery of virulence factors, horizontal transfer of antibiotic resistance gene. *A. baumannii* NfuA Fe-S scaffold protein, that participates in the formation of Fe-S clusters and plays a role in cell responses to iron chelation and oxidative stress, has also been identified as a virulence factor. Several protein secretion systems have been identified in *A. baumannii*. The most recently described *A. baumannii* secretion system is a Type II Secretion System (T2SS). β-lactamase PER-1 has been suggested to be an *A. baumannii* virulence factor. PER-1 is an ESBL, but this gene is associated with cell adhesion. CipA-binding plasminogen is converted to active plasmin that degrades fibrinogen and complement C3b, which contributes to serum resistance of *A. baumannii*.

Antimicrobial resistance of *A. baumannii*

1. Beta-Lactamases (VIM/IMP):
   Inactivation of β-lactams by β-lactamases is a major antibiotic resistance mechanism in *A. baumannii*. Based on sequence homology, β-lactamases are grouped into molecular classes, A, B, C and D (β-lactamase genes: *bla*OXA-23, *bla*OXA-24, *bla*OXA-58, *bla*OXA-51, *bla*TEM, *bla*SHV, *bla*CTX-M, and *bla*PER)

2. Efflux Pumps:
   Efflux pumps are associated with resistance against many different classes of antibiotics, such as imipenem and tigecycline, in *A. baumannii*. The TetB efflux pump is the main determinants of minocycline resistance.
3. Permeability Defects:
   A change in envelope permeability can influence antibiotic resistance. For example, porins form channels that allow transport of molecules across the outer membrane
4. Aminoglycoside - Modifying Enzymes:
   Aminoglycoside-modifying enzymes are the major mechanism by which *A. baumannii* confers resistance to aminoglycosides.
5. Alteration of Target Sites:
   Modifications in antibiotic target sites for antibiotics can induce antibiotic resistance in *A. baumannii*. In the absence of other known resistance mechanisms, only overexpression of altered PBPs with a low affinity for imipenem induces imipenem/carbapenems resistance.
6. AdeABC is associated with decreased susceptibility to tigecycline. Quinolone resistance is associated with modifications in GyrA (one subunit of DNA gyrase)
7. Change in affinity for binding was seen in case of colistin resistance
8. The changes in the membrane binding and changes in bacterial targets due to point mutations in gyrA and parC topoisomerase enzymes confer resistance against quinolones

MDR-AB:

MDR-AB is defined as an *A. baumannii* strain resistant to at least three different groups, penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones and aminoglycosides, has emerged and has been reported worldwide to significantly increase the morbidity, mortality, and cost of treatment. The incidence of MDR-AB is increasing worldwide. *Acinetobacter* spp exhibit multidrug resistance through production of β-lactamases, alterations in Outer Membrane Proteins (OMPs) and Penicillin-Binding Proteins (PBPs) and increased activity of efflux pumps. Resistance to β-lactams appears to be primarily caused by production of β-lactamases which include ESBLs, MBLs and oxacillinases. MBLs are classes of powerful enzymes called carbapenemases responsible for antibiotic resistance. Four groups of these enzymes have been described in *A. baumannii*, including IMP-like, SIM-1, NDM-type, and VIM-like carbapenemases. MBLs-encoding genes are located on integrons that can be transmitted from one bacterial species to another. ESBLs are encoded by TEM-type, SHV-type, and CTX-M-type genes; they are resistance to penicillins and third-generation cephalosporins. The drug of choice to treat nosocomial infection caused by MDR-AB is the carbapenems. However, there is an increasing rate of carbapenem-resistant *A. baumannii* around the world. *Acinetobacter* species are distinguished for their intrinsic resistance to antibiotics and for their ability to acquire genes encoding resistance determinants like, production of β-lactamases, aminoglycoside-modifying enzymes, diminished expression of outer membrane proteins, mutations in topoisomerases, and up-regulation of efflux pumps play an important part in antibiotic resistance. The accumulation of multiple mechanisms of resistance leads to the development of multiply resistant or even "panresistant" strains [11]. *A. baumannii* is labeled as MDR-AB when it

is resistant to more than two of the five classes of antibiotics [cephalosporins (ceftazidime or cefepime), carbapenems (imipenem or meropenem), Ampicillin/sulbactam, Fluoro-quinolones (ciprofloxacin or levofloxacin) and Aminoglycosides (gentamicin, tobramycin, or amikacin)]. Carbapenems were considered as the most important agents for the treatment of infections caused by MDR-AB. Carbapenem Resistant *A. baumannii* (CRAB) is now emerging as a potential threat and it is usually resistant to almost all antimicrobial classes except colistin and tigecycline. The most important mechanism of CRAB is enzyme inactivation by the production of β-lactamases, which hydrolyze the carbapenams. These hydrolyzing enzymes include MBL and class D β-lactamases (widespread). The main gene clusters responsible for this resistance are *bla*OXA-23-, *bla*OXA-24/40- and *bla*OXA-58-like gene clusters, identified either in the chromosome or in plasmids of *A. baumannii* strains [8]. Colistin is the last resort for treatment of multidrug-resistant *A. baumannii*. Unfortunately, resistance to colistin has been reported all over the world. The highest resistance rate was reported in Asia, followed by Europe. The mechanism of resistance might be loss of lipopolysaccharide or/and the PmrAB two-component system [12].

Genotype and phenotype of MDR *A. baumannii* in patients with VAP:

Different genotypes and phenotypes were reported by various studies from India and overseas. Royer *et al* reported all CRAB carbapenem isolates of *A. baumannii* were OXA-23 producers [Molecular typing: clone A (clinical) and H (surface)] [13]. Baker *et al.* reported production of carbapenemases MBLs in *Acinetobacter* (blaVIM2) [14]. Patro *et al.* and Khelgi *et al.* quoted AmpC β−lactamase and MBL was positive MDR-AB with VAP [7, 15]. Joseph *et al* and Khurana *et al*. noted ESBL, AmpC and carbapenemase genes in their study of MDR *Acinetobacter* spp [16, 6]. Banerjee *et al.* (2018) reported significant patients with Hospital Acquired Pneumonia (HAP) with MDR *Acinetobacter* spp. with imipenem resistance in majority of isolates (bla_{IMP}, bla_{VIM}, bla_{NDM-1} and $bla_{OXA-23-like}$ genes) [17]. Ghada *et al.* observed carbapenems resistant isolates were positive for *bla*OXA-51- like gene, *bla*OXA-23 like gene, *bla*OXA-58 among MDR isolates of *Acinetobacter* [18]. Dey *et al.* reported AmpC β-lactamases and MBLs producing *Acinetobacter* isolates in their study [19]. Thakuria *et al.* (2013) and De *et al.* (2018) concluded that there was carbapenemase producers showed high degree of cross resistance to antibiotics (46%) in their cohort [20, 21]. Goel *et al.* (2012) found presence of MBLs in 62.96% of *A. baumannii* isolates [22]. Karampatakis *et al.* (2017) reported carbapenem-resistant (CR) strains with VIM and OXA-23 carbapenemases [23]. Singh *et al* in their study stated that, the gene clusters responsible for this resistance were *bla*OXA-23-, *bla*OXA-24/40 and *bla*OXA-58-like gene clusters [8]. Srinivasan *et al* observed presence of *bla*OXA-23 and IS*Aba1* linked *bla*OXA-66 in *Acinetobacter* spp. with imipenem resistance. MDR had *bla*ADC-25, class 1 integron-borne aminoglycoside modifying enzymes and sense mutations in *gyrA*/*parC* and active efflux (*adeB* efflux gene) [24]. *Fatma et al.* reported meropenem resistance was associated with AmpC β-lactamase, MBLs and Efflux pump *Acinetobacter* isolates. *Ramoul et al.* reported *bla*OXA-51, *bla*OXA-23 and *bla*TEM-1 gene in their *Acinetobacter* isolates [4]. Ganjo *et al.* quoted *A. baumannii* with $bla_{OXA-23-like}$ and $bla_{OXA-24-like}$ gene with majority of $bla_{OXA-23-like}$ isolates had the

ISAba1 insertion sequence which is responsible for carbapenem resistance [25]. Mohammad *et al.* reported presence of types A, B, C, D, E, *tet A* and *tet B* genes in their study of *A. baumannii* isolates [26]. European clones I to III, carbapenem-resistant genotypes and novel international clone was quoted by Petersen *et al.* [27]. Production of class D OXA carbapenemases and class B MBL plays a predominant role in contributing to carbapenem resistance to *A. baumannii* worldwide (Fig. 1).

Prevalence of MDR-*Acinetobacter* VAP:

Various factors affect the incidence of MDR VAP due to *A* spp. including, criteria, ICU protocols, implementation of VAP bundle, ICU setting and antimicrobial policy. The rate of MDR VAP due to *A. baumannii* is more in developing countries as compared to western world and developing country. [28, 15, 6, 17, 29, 31, 32, 4, 14, 26, 33, 18, 34, 21, 19, 35, 7, 25, 36, 37, 38] (Fig. 2).

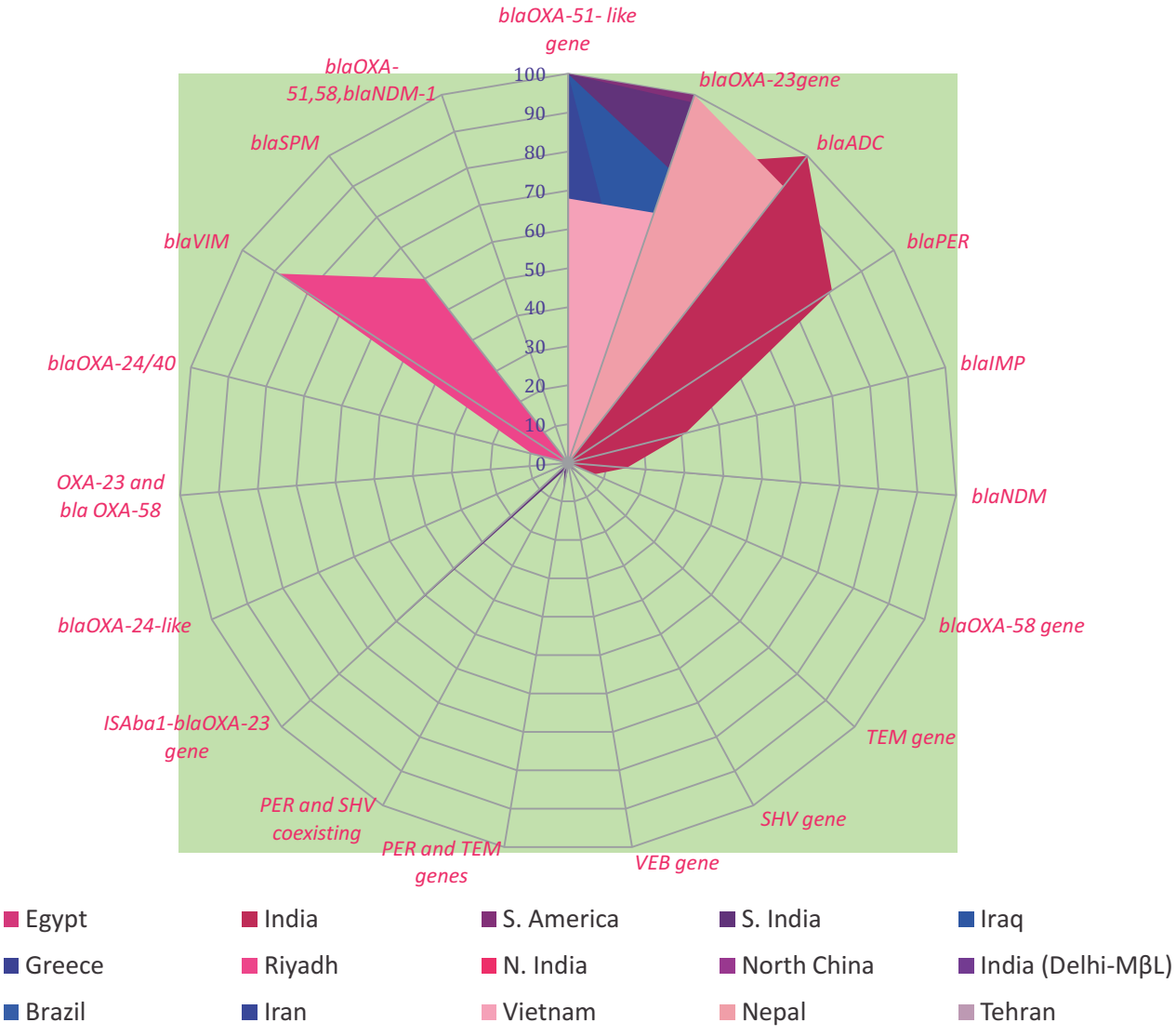

Fig. 1: Prevalence of Various Genotypes in Various Studies

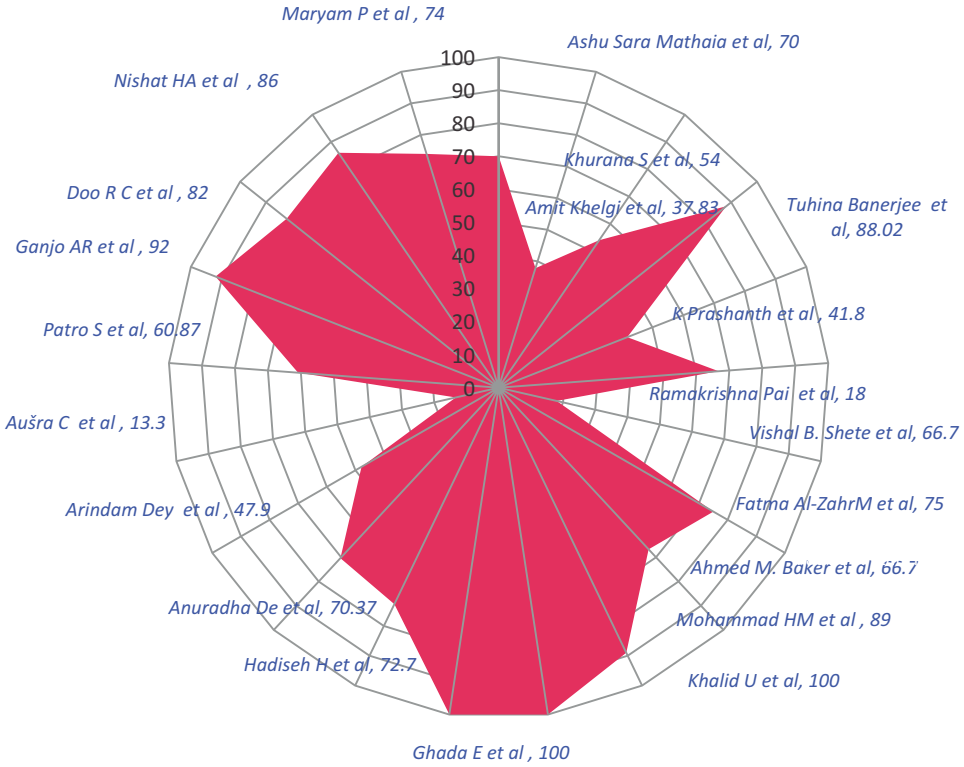

Fig. 2: Prevalence of MDR *Acinetobacter* in Various Studies

Drugs Resistance Pattern of MDR-AB in VAP:

A. baumannii is an opportunistic pathogen with increasing clinical significance, particularly in intensive care patients, causing nosocomial infections including VAP. The organism has the potential to persist in hospital milieu for many days. Many *Acinetobacter* spp are resistant to frequently used antibiotics like aminopencillins, ureidopencillins, cephalosporins and amino-glycosides. Carbapenems, β-lactam/β-lactamase inhibitor combinations and tetracyclines like minocycline and tigecycline and colistin are the commonly used against severe *A. baumannii* infections. Fatma *et al* (2014) (Egypt) reported 75% of MDR-AB isolates. *A. baumannii* exhibited high resistance rate to imipenem (66.6%), meropenem (73.3%) and cefazolin and cephalothin (100%) with moderate susceptibility to tetracycline (40%) and gentamicin (33.3%). Total 44.4% *A. baumannii* were positive for AmpC β-lactamase and 55.6% for MBLs. The efflux pump was detected in 77.8% of isolates [4]. Srinivasan *et al.* (2009) quoted MDR- AB in 79.5% with (*bla*OXA-23 in 13% and IS*Aba1* linked *bla*OXA-66 in 79.5%) isolates with high level imipenem resistance. The OXA producing isolates, had multidrug resistance by *bla*ADC-25, class 1 integron-borne aminoglycoside modifying enzymes, presence of sense mutations in *gyrA*/*parC* and involvement of active efflux (with evidence for the presence of *adeB* efflux gene) [24]. Karampatakis *et al.* (2017) reported Carbapenem-resistant (CR) strains, VIM and OXA-23 carbapenemases among *A. baumannii* [23]. Royer *et al.* (2015) (Brazil) reported that, the

VAP caused by carbapenem resistant *A. baumannii* (OXA-23) [13]. Ramoul *et al.* (2013) reported that, the *A. baumannii* are resistant to all β-lactams (*bla*OXA-51 gene, *bla*OXA-23 and *bla*TEM-1 [39]. Mohammad *et al.* (2014) Iran quoted, 89% of *A. baumannii* were resistant to tetracycline 35% to Minocycline 25% to doxicycline and were sensitive to tigecycline [tet B (87.6%) and *tet* A (2.2%) genes and coexistence of *tet* A and tet B (1.1%)]. Distribution of REP-types among *A. baumannii* isolates was types A (40%), B (30%), C (10%), D (5%) and E (5%). They concluded that, *tet A* and *tet B* genes play an important role in the induction of resistance for tetracyclines [26].

The various studies have reported the drug resistance to Carbapenem, β−lactam and Tetracycline for *A. baumannii* [13, 14, 6, 17, 16, 36, 40, 38, 18, 19, 20, 31, 41, 4, 25, 26]. We compared the various studies in reference to incidence, risk factors, genotype, phenotype, drug resistance pattern, preventive strategy of MDR-Acinetobacter associated ventilator associated pneumonia in different parts of the world (Table 1).

Table 1: Comparison Prevalence, Risk Factors, Genotypes of MDR Acinetobacter Associated with VAP

References	Type of study	Patients (n)	Prevalence of VAP & MDR-*Ab*	Risk factors for VAP	Phenotype and genotype
13	Cohort of (14 months)		carbapenem resistant A*b*.	Trauma and inappropriate antimicrobial therapy	All carbapenem resistant were OXA-23 producers; Molecular typing: clone A (clinical) and H (surface)
14	Prospective	117 *Acinetobacter* spp. (10.6%)	66.7% resistant to imipenem (MBL producers)	Production of carbapenemases 15.1% of A*b*: blaVIM2	Production of carbapenemases, especially MBLs. *Acinetobacter* isolates were highly resistant: 80.8%
7	Cross−sectional study (2 years)	100	The prevalence of VAP was 35% MDR: 60.87%	*Acinetobacter* spp. 10 (31.25%), AmpC β−lactamase: 35.29%. MBL: 17.64%. *Acinetobacter* spp. showed 100% resistance to ceftazidime, amikacin and ciprofloxacin	
28	Retrospective	n=108 (A*b*: 6.85%)	MDR: 70%	Risk factors: Duration of intubation and inappropriate antibiotics; Crude mortality rate was over 70%	
15		120 33 patients had VAP	VAP with MDR pathogens (Ab) spp: 37.83%	MBL AmpC β-lactamases	MBL was produced by 44.44% of *Acinetobacter* spp and AmpC β-lactamases 71.43%

References	Type of study	Patients (n)	Prevalence-of VAP & MDR-*Ab*	Risk factors for VAP	Phenotype and genotype
6	5−year period	of VAP 11.9/1000 days	*A. baumannii* (54%)	A high rate of MDR ESBL, AmpC and carbapenemase genes	
16	Prospective (15 months)			*Acinetobacter* spp: late-onset VAP	Production of ESBL, AmpC β lactamases and MBL
17	A laboratory-based audit 5 years	993 cases (100) isolates of A*b.*	88.02% MDR and 61.97% XDR	Longer duration of hospital stay: 88.02% MDR and 61.97% XDR	VAP resistant to imipenem and 88.02% MDR and 61.97% XDR. (bla_{IMP} (89%), bla_{VIM} (51%), bla_{NDM-1} (34%), & $bla_{OXA-23-like}$ (93%) genes)
18	Descriptive, cross-sectional	44	*A. baumannii* isolates (100%) were (MDR).	Age>40, Length of hospital stay, Prior use of antibiotics	Carbapenems resistant isolates: *bla*OXA-51- like gene, *bla*OXA-23 like gene, *bla*OXA-58, Colistin sensitivity: 93.2%
19	Prospective	97	VAP: 45.4% and MDR Ab: (47.9%)	Stress-ulcer prophylaxis, use of antibiotics, Re-intubation	30.43% *Acinetobacter* spp : AmpC β lactamases and MBLs: 21.74%
21	Cross-sectional	130	VAP: 40.8%, late-onset VAP: 81.13%	Diabetes mellitus, advancing age (>60 yrs), COPD	*Acinetobacter* spp:33.96% Carbapenem resistance: 46% MDR-A*b*: 70.37%
29	Retrospective	43 (two-year)	*Ab:* 41.8%	Resistant antibio-type, MV	Most of *A. baumannii* isolates were MDR.
20	Prospective one year	100	*A. baumannii*: 7.55%		Carbapenemase producers showed cross resistance
42	Retrospective	134	*Acinetobacter* spp. (60%)		Mortality : 46%
31	Prospective	60	head injury, cerebral hemorrhage and COPD		MDR-AB VAP cases: 11.6%

References	Type of study	Patients (n)	Prevalence-of VAP & MDR-*Ab*	Risk factors for VAP	Phenotype and genotype
40	Prospective		VAP was 42.5% MDR-AB: 66.7%		GNB:78.6% *A. baumannii*: 32.1%
30	Prospective	95	40.1 VAP infections/1000	Longer ICU stay Elderly patients	*Acinetobacter* species: 53.2% MDR:27.3%
43	Prospective	VAP 4.1-25.3/1000 Days			*A. baumannii*: 100%. MDR:55%-76%
34	Retrospective	132	MDR 72.7%	Increased ICU stay and longer intubation time	
32	Cross-sectional	100 patients	VAP: 44.2% A*b.* :18%	Age, COPD, DM, MOF, duration of MV	*Acinetobacter* spp were the most resistant pathogens
44	Retrospective	54	Male, high APACHE II score, renal failure and low platelet		Mortality was developed in 70%.
45	Prospective (13 months)	202	VAP: 14.85% (23.2 VAP/1000 VD	Reintubation and tracheostomy prolonged duration of mechanical ventilation, ICU stay associated with MDR-AB (48.21%)	
22	Prospective	53	MDR-AB 49.09%		MBLs: 62.96%
46	Prospective (10 mths)	140 patients 28 (20%) develope d VAP.	VAP was 21.875 per 1,000 ventilator days.	Prior antibiotic therapy, hospitalization and MV, supine head position, reintubation unconsciousness	late onset VAP: 60.7% *Acinetobacter* spp. with late onset VAP, MDR: 69.7%, MBL: 30.23%, MBL- 50%
35	Retrospective cohort study two-year	60	MDR: 13.3% XDR: 68.3%	Higher SAPS II score, increased hospital LOS prior to ICU, MV, Carbapenem use; mortality due to drug-resistant *A. baumannii* VAP was high; Potentially pandrug resistant:18.3%	
23	Cross-sectional (18 month)	(56) CARB resistant	VIM and OXA-23 carbapenemases *A. baumannii* (88.9 %). *A. baumannii* displayed phenotypic diversity in AMK, GEN, SXT, tobramycin and rifampicin (8 clusters).		

References	Type of study	Patients (n)	Prevalence-of VAP & MDR-*Ab*	Risk factors for VAP	Phenotype and genotype
8	Review		Gene clusters responsible for this resistance are *bla*OXA-23-, *bla*OXA-24/40-, and *bla*OXA-58-like gene clusters		
24	Cross-sectional	83	*bla*OXA-23 and IS*Aba1* linked *bla*OXA-66: high level imipenem resistance; MDR: *bla*ADC-25, class 1 integron-borne aminoglycoside modifying enzymes, presence of sense mutations in *gyrA* /*parC* and involvement of active efflux (with evidence for the presence of *adeB* efflux gene). MDR:79.5%		
4	Cohort	72	Carbapenem resistant: 45 MDR- A*b*: 75%	AmpC β-lactamase: 44.4% positive; MBLs: 55.6%-carbapenem resistance; Efflux pump: 77.8%; MBLs and AmpC β-lactamase: meropenem resistance	
39	Cohort (15 month)	23	β-lactams resistant: 19	*bla*OXA-51 gene was found in all isolates, *bla*OXA-23: 14 and *bla*TEM-1 in:3	
35	Cohort (21 months)	120	IMP resistant: 92%	*A. baumannii*- carried $bla_{OXA-23-like}$ gene and $bla_{OXA-24-like.}$ All 101 $bla_{OXA-23-like}$-positive isolates had the ISAba1 insertion sequence, $bla_{OXA-23-like}$ gene for carbapenem resistance	
26	Cross-sectional (2 years)	100	89% were resistant to tetracycline 35% to Minocycline 25% to doxicycline All isolates were sensitive to tigecycline		Types A (40%), B (30%), C (10%), D (5%) and E (5%). *tet A* and *tet B* genes
47	Prospective (1 year)	105 VAP: 57.14%	VAP 31.7/1000 day	Duration of MV Trauma	*Acinetobacter* spp: 34.28% Mortality: 48.33%
33	Descriptive	74	MDR: 100%	head trauma and stroke	*A. baumannii* : 21.0%
36	Muticentric	2,445	*Acinetobacter*: 67.3% Imipenem resistance; MDR: 82%, XDR: 51.1%		*Acinetobacter* spp were the most frequent isolates
48	Prospective (20 months)	84	VAP rates 6.242/ 1000	Mortality: 61.84%	*A. baumannii*: 37.63% Majority of them were MDR
49	Prospective (2 yrs)	144	Early-onset VAP: 24.3% ; Late-onset VAP: 26.4%		*Acinetobacter* spp was the most common pathogen in VAP

References	Type of study	Patients (n)	Prevalence-of VAP & MDR-*Ab*	Risk factors for VAP	Phenotype and genotype
27	Cross-sectional	65	Higher APACHE II scores		European clones I to III, Carbapenem-resistant (novel)
37	Cross-sectional	66	*Acinetobacter*: 26%		MDR: 86.36%
50	Review article 8 (2008-2014)	High rate of resistance to all antibiotics		Increase in imipenem and meropenem resistance from 2010-2011 and 2012-2013	
41	systematic review of 41 studies			CRAB: 64.91%; MDR-AB: 58.51%	
38	IR-MDR *A. baumannii*	55% of *A. baumannii* isolates were resistant to imipenem, and 74% had a MDR phenotype		Kuwait (42%), Pakistan (100%), Turkey (98%), UAE (76%), and Saudi Arabia (63%).	

Risk factors for developing MDR-VAP due to *Acinetobacter* spp:

VAP affects just about 30% of intubated mechanically ventilated patients in ICUs worldwide. Advancing age, male gender, trauma, cerebral hemorrhage, impaired consciousness, higher APACHE II scores, higher SAPS II score, increased hospital stay prior to ICU, prolonged duration of MV, supine head position, prior antibiotic therapy, inappropriate antimicrobial therapy, carbapenem use, longer intubation time, reintubation, tracheostomy renal failure COPD, DM, MOF, stress ulcer prophylaxis and low platelet were found to be associated with the risk of MDR-AB. Occurrence of MDR, XDR and pan-resistant *A. baumannii* has been observed in ICU settings. Risk factors associated with the resistance acquisition mainly include injudicious and broad spectrum antibiotic exposure, prolonged stay in the ICUs, mechanical ventilation and drifting from local antibiogram based antibiotic policies. Investigations of several outbreaks of resistant infections have been recognized to direct contact (bacterial flora of moist regions of skin like axilla and groin). The contamination of hands of Health Care Workers (HCW) occurs even after minor contact with colonized patients [13, 28, 16, 17, 18, 19, 21, 29, 31, 30, 34, 32, 45, 35, 47, 27, 46].

Incidence of VAP and MDR *Acinetobacter*:

Patro *et al* (2018) in their study quoted 35% VAP rate with *Staphylococcus aureus* were common in early-onset VAP and nonfermenters in late-onset VAP with 60.87% were MDR *Acinetobacter* and positive for AmpC β−lactamase and MBL. *Acinetobacter* spp. showed 100% MDR and sensitive to polymyxin B and tigecycline [7]. A study from India quoted VAP rate of 11.9/1000 VDs with MDR-AB (54%) with presence of ESBL, AmpC and carbapenemase genes [6]. Rit *et*

al (2014) reported 21.875 per 1,000 ventilator days (20%) incidence rate of VAP (*Acinetobacter* spp. MBL: 30.23%) [46]. John *et al* reported 14.85% (23.2 VAP episodes per 1000 ventilator days) incidence of VAP (MDR-AB: 48.21%) [45]. Goel *et al.* quoted MDR-AB (49.09%) were the most common pathogens isolated producing MBLs [22]. Khalid *et al* reported MDR-AB*i* associated VAP were 100% resistant to ampicillin/sulbactam, piperacillin, cefuroxime [33]. A study from North India by Banerjee *et al.* quoted high prevalence of *Acinetobacter* related Hospital Acquired Pneumonia (HAP) with resistance to imipenem (bla_{IMP} , bla_{VIM} , bla-NDM-1 and $bla_{OXA-23-like}$ genes) [17]. Pai *et al.* (2012) VAP was found to be 44.2% of patients. *Acinetobacter* species were the most resistant pathogens with high mortality [32]. Ghada *et al.* in their study stated that, all *A. baumannii* isolates were multidrug resistant and 75% were resistant to carbapenems but were sensitive to colistin (93.2%) (*bla*OXA-51- like gene, *bla*OXA-23 like gene, *bla*OXA-58) [18]. Dey *et al* reported incidence of VAP was found to be 45.4% among the mechanically ventilated patients with 47.9% MDR-*Acinetobacter* spp (AmpC β lactamases MBLs) [19]. Thakuria *et al.* reported 51%VAP rate with *A. baumannii* were carbapenemase producers [20]. A study from North India, quoted *A. baumanii* in 20.9% with VAP. The incidence of VAP in Indian ICUs is ranged from 30% to 73%. Compared to Western data, Gram negative organisms are the most common etiological agents in both early and late VAP in India [51]. Kumari *et al* reported VAP rate of 13% with predominance of Gram negative organisms including *Acinetobacter* spp. (13, 21%) [42]. Shaik *et al.* quoted that, the late onset VAP (60.8%) predominated by Gram negative Bacteria (MDR-AB: 32.1%) [40]. Mathai *et al* reported VAP rate of 38% (40.1 VAP infections/1000 ventilation days) predominantly caused by GNB (*Acinetobacter* species: 53.2%) with 27.3% of isolates demonstrated multidrug resistance [30]. Asir *et al* reported Incidence of VAP 15.2/1000 ventilator days (*A. baumannii*: 100%) [43]. Karampatakis *et al.* (2017) stated that, OXA-type carbapenemases are present with highest prevalence worldwide of them bla OXA-23-like, bla OXA-58-like and VIM are the most important genes found in Greece [23]. Ganjo *et al.* (2016) (Iraq) reported 100% of *A. baumannii* isolates had $bla_{OXA-51-like}$ genes ($bla_{OXA-23-like}$ gene, $bla_{OXA-24-like}$ genes VIM and IMP MBLs $bla_{OXA-58-like}$, upstream ISAba1 insertion) [25]. Ghosh *et al.* (2018) (India) quoted VAP rate of 6.242/ 1000 ventilator days with mortality of 61.84%. *A. baumannii* (37.63%) was the commonest organism isolated [48]. Doo *et al.* (2011) in their multicentric study stated that, major bacterial isolates from VAP cases in Asian countries were due to *Acinetobacter* spp. (MDR: 82% and XDR: 51.1%) [36]. Ranjan *et al.* (2014) quoted 57.14% (VAP was 31.7/1000 ventilator days) incidence of VAP in their study (*Acinetobacter* spp: 34.28%) [47]. Aušra *et al.* (2019) quoted 13.3% MDR, 68.3% XDR and 18.3% potentially pandrug-resistant *A. baumannii* [35]. Teerawattanapong *et al.* (Southeast Asia) (2018) in their systematic review of 41 studies found that, a cumulative incidence of HAI caused by *A. baumannii* in Southeast Asia was substantially higher with carbapenem-resistance (64.91%) [41]. Maryam *et al* (2016) in their meta-analysis (2016) of Imipenem-resistant MDR *A. baumannii* observed that, the 55% imipenem

resistance [38]. Moradi *et al.* in their review article of 87 papers (2008-2014) from Iran observed an increase in antimicrobial resistance in MDR-AB isolates [50]. Mathaia *et al.* (2012) late-onset VAP developed in 76.85% due to *Acinetobacter* (MDR-AB: 70%) [28]. A study from India stated that the production of AmpC β-lactamases and MBLs were responsible for the MDR *Acinetobacter* spp and associated with late-onset VAP (MBL: 20% and AmpC β-lactamases: 60.7%) [16]. Ahmed *et al*. in their study, isolated 80.8% MDR *Acinetobacter* with Imipenem-resistant (MBL producers blaVIM2) [14]. De *et al.* (2018) quoted 40.8% incidence of VAP (late-onset VAP: 81.13%) caused by MDR-*Acinetobacter* spp (70.37%) and were carbapenem resistant [21]. *Khelgi et al.* (2017) reported 27.5% of patients to have VAP (*Acinetobacter* spp.37.83%) producing MBL and AmpC β-lactamases. ICU infections are important cause of mortality and morbidity. Globally Gram positive organisms are prevalent in ICUs, where as Indian ICUs are overwhelmed with Gram negative organisms including MDR-*Acinetobacter* spp [15]. *Acinetobacter* are among the most notorious bacteria isolated in hospital infections, particularly in developing countries. Combined therapy has been an alternative for multi-drug-resistant *Acinetobacter*. Tigecycline and colistin can be valuable therapeutic options for the treatment of MDR-*Acinetobacter* infections [52]. Treatment options are limited; carbapenems and colistin are the current agents of choice for the most drug-resistant infections [8]. Upcoming promising drug strategies are new β-lactamase inhibitors, Inhibitors of aminoglycoside-modifying enzymes and multidrug efflux pumps, ukaryotic antimicrobial peptides. To manage patients with VAP comprehensively, requires a multi-disciplinary team effort and approach of clinical microbiologists, physicians and hospital infection control associate.

Conclusion:

Multi-drug, extended-drug or pan-drug resistance makes treatment a real medical challenge in MDR-VAP due to *Acinetobacter*. Inadequate infection control facilities and policies, lack of resources, ignorance for preventive strategy are the main reasons for the rise of MDR organisms in ICU settings. The periodic active surveillance of the ICU environment including the ventilator circuits, respiratory therapist may cut down the significant proportion of ventilator associated pneumonia. There is pressing need to implement an antimicrobial stewardship program supported by the local microbial data integrated with international guidelines to optimize the antimicrobial use may improve outcomes in patients with VAP due to MDR-*Acinetobacter*. The genotype $bla_{OXA\text{-}23\text{-}like}$ and $bla_{OXA\text{-}51\text{-}like}$ genes are the most prevalent genotype in various studies. The a surveillance program of ICU acquired infections, antibiotic usage and molecular typing of MDR *A. baumannii* isolates may help for making hospital antibiotic policies. The empirical therapy should be broadened (anti-pseudomonal cephalosporin, carbapenem, or β lactamase inhibitor plus fluoroquinolone, or aminoglycoside plus linezolid) to cover the most probable pathogens including MDR. Tigecycline and colistin should be reserved for resistant cases. Mortality in VAP cases is high due to the increasing incidence of multidrug-resistant organisms in ICUs. Various studies emphasized on

appropriate use of antimicrobial therapy to fight against these MDR-*Acinetobacter* pathogens.

Key Message:

Judicious use of antimicrobials, rotational antibiotic therapy, novel preventive, treatment strategies, antibiotic recycling, combinations of antibiotic and development of novel antimicrobial agents will be beneficial to fight against MDR-AB causing ventilator associated pneumonia at large. Early and correct diagnosis of VAP is a challenge for choosing an optimal antibiotic treatment and cure.

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