MULTI DRUG RESISTANCE ACINETOBACTER BAUMANNII: A SYSTEMATIC REVIEW FOR MICROBIAL AND CLINICAL STUDY

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ABSTRACT: Infections due to Multi drug resistance Acinetobacter baumannii is now recognized as a major public health problem worldwide. The nosocomial infection due to Multi Drug Resistance Acinetobacter baumannii has leaded to increased in morbidity and mortality which has added noticeably to significant challenge to modern antibiotic therapy system. This is due to rapid phenomenon of Acinetobacter baumannii to acquire antibiotic resistance. Thus, in this review the overview of current knowledge on epidemiology, infections, mechanism of resistance and effective treatment options are briefly highlighted.

Key words: Acinetobacter baumannii, multidrug-resistance, Carbapenem, β-lactamase, infections.

INTRODUCTION
The emergence of Multi Drug Resistance (MDR) Acinetobacter baumannii is the major cause of nosocomial infection associated with a significant morbidity and mortality (Joly-Guillou, 2005 and Perez et al., 2007). Currently, Multi drug Resistance (MDR) A. baumannii are being increasingly isolated from the clinical samples worldwide has challenge to the antibiotic era (Paterson, 2006; Zavascki et al., 2010; Dio et al., 2009; KO et al., 2007 and Maviglia et al., 2010). The rapid emergence and global dissemination of A.baumannii resistance patterns have suggested to the present era that antibiotic therapeutic system is going to terminate soon with Acinetobacter species rather than other bacteria such as Methicillin Resistance Staphylococcus aureus (MRSA) (Hanlon,2005). Thus, this review reports the summarize form on the history, epidemiology, and infection caused by A. baumannii as well as the current mechanism of resistance to selected antibiotics and current strategies in therapeutic efforts and control of infection caused by multidrug resistance A. baumannii.

HISTORY
Acinetobacter species are gram negative; coccobacilli with G+C content of 39 to 47%. They are strictly aerobic, non-motile, catalase positive, oxidase negative and can grow on usual laboratory media (http://microbewiki.kenyon.edu/index.php/Acinetobacter_baumannii, Koneman et al.,1997, Wyant et al.,1996 and Von Graevenitz,1995).The genus Acinetobacter was first named in 1911 (http://en.wikipedia.org/wiki/nosocomial infection). Due to lack of standard microbiological techniques of nomenclature until early 20th century, Acinetobacter is known with different names such as Herellea vaginicola, Bacterium anitratum and Mima polymorpha.
In the early 20th century taxonomic history of *Acinetobacter* species have been assigned in family Neisseriaceae with genera *Neisseria*, *Kingiella* & *Moraxella*. Now, in current taxonomic history of *Acinetobacter* species, they have moved from family Neisseriaceae to the family Moraxellaceae under the names *Moraxella*, *Herellea*, *Mima Achromobacter* and *Alcaligene* (Maviglia, 2010; Von Graevenitz, 1995 and Wong, 1990). Even today, the *Acinetobacter* species is in verse of controversy and undergoing continuous changes. The use of molecular techniques like DNA/DNA hybridization, PCR, PFGE has established 33 different ‘genomic species’ belonging the genus *Acinetobacter* of which 18 have now have been assigned name and further 28 unnamed groups and also 21 ungrouped single bacterial strains (Dijkshoom and Nemec, 2008). Studies have revealed that *Acinetobacter baumannii* rank in genospecies 2 (Koneman et al., 1997, Wyant et al., 1996 and Dijkshoom and Nemec, 2008) with the biochemical characteristic described by Sofia Constantiniiu, et al (Sofia Constantiniiu et al., 2004). In clinical setting *Acinetobacter baumannii* cannot be separately identified from genospecies 3 and genospecies 13TU so together called as *A.calcoaceticus-A.baumannii* complex (Gerner-Smidt et al., 1991; Bergogne-Berezin and Towner, 1996; Van Looveren et al, 2004 and Peleg et al., 2008).

**EPIDEMIOLOGY**

*Acinetobacter* are ubiquitous in nature and have been isolated from soil, water, animals, human & significantly in hospital environments leading to outbreaks as the organism can survive long on dry inanimate surfaces even up to five months in condition including dried and moist environment(Henriksen,1973; Paterson,2006; Boerlin, et al.,2001; Somor et al., 2002 and Denton et al.,2005). A propensity to tolerate various environmental stresses and its wider range of resistance determinants renders it to be a successful nosocomial pathogen(Maragakis and Perl,2008). At present, MDR *Acinetobacter baumannii* has emerged as significant problem worldwide (Gould, 2008). There are some reports that describe the MDR *A.baumannii* as challenge to the modern era from Europe, North America, South America, South Pacific Asia & Australia (Perez et al., 2007; Van Looveren, 2004; Lee, 2004 and Van Dessel, 2004). The rising evidence of MDR *Acinetobacter baumannii* infection has led to the several outbreaks (Reiner et al., 2007 and van den Broek et al., 2006). To distinguish these outbreak several moderns epidemiological typing tool are being used which include plasmid profiles analysis, Pulse Field Gel Electrophoresis (PFGE), ribotyping, Amplified Fragment Length Polymorphism (AFLP), PCR-based tests and multilocus sequence typing (Abbo, 2005; Go, 1994 and Maslow, 2005).

The common potential sources for the colonization and transmission of MDR *Acinetobacter baumannii* at the variety of affected patients includes ventilators, suctioning equipment, mattresses, pillows, humidifiers, bed rails, bedsides, containers of distilled water, urine collection jugs, intravenous nutrition equipment, potable water, reusable arterial pressure transducers, the knobs of electrocardiographs, wash basins, infusion pumps, sinks, hygroscopic bandages, showers stainless-steel trolleys, resuscitation equipment and tables, soap dispensers, bed linen, portable radiology equipment, spinometers, temperatures probes and multi-dose nebulizers, computer keyboards, health care workers with damaged skin, pumps, pressure transducers, hemofiltration systems, cell phone, blood pressure cuffs, pulse oximeters, laryngoscope blades, door handle, nasogastric feeder and ventilator rinsing (Paterson,2006 and Karageorgopoulos,2008). Furthermore certain type of procedure for the treatment of patients such as hydrotherapy or pulsative lavage treatment of wounds, specific surgical interventions, cauterization and tracheotomy (Maragakis et al., 2004; Ayan et al., 2003 and del Mar Tomas, 2005) constraints *Acinetobacter baumannii* along with geno species 3 & genospecies 13TU are the most frequently found species in human clinical specimen (Tjernberg. and Ursing, 1989; Gerner-Smidt &Tjernberg, 1993 and Berlau et al., 1999). Whereas other *Acinetobacter* species such as *Acinetobacter junii*, *Acinetobacter johnsonnii*, *Acinetobacter radioresistens* and geno species 15BJ are found in lower frequencies (Berlau et al., 1999 and Seifert et al., 1997). In constraints to the colonization on hospital setting there are few available data in the non clinical environmental occurrence of *Acinetobacter baumannii*: gen.sp.3 and gen.sp.13TU are present in vegetable, food, arthropods, meat, soil, water & rice (Huys et al.,2007a; Huys et al 2007b; Fournie and Richet, 2006 and Raoul, 2004).
ACINETOBACTER BAUMANNI INFECTION:

PATHOGENESIS

The actual mechanism of pathogenicity is unclear but different genomic and experimental studies have identified virulence genes involved in pilus biogenesis, iron uptake and metabolism, quorum sensing and type IV secretion system (Vallenet et al., 2008). Although nematode model are used to screen the potential virulence genes but novel genes in Acinetobacter baumannii with significant role in pathogenicity that have yet to be assessed in mammalian model (Smith et al., 2007). The initial step in the colonization, infection and epidemic spread of Acinetobacter baumannii is adherence of both biological and abiotic surfaces on which it is stable to form biofilms (Lee et al., 2008 and Vidal et al., 1996). The pili and hydrophobic sugars in the O-side-chain moiety of lipopolysaccharide (Haseley et al., 1997) promote adherence to host cell. The LPS is a potent inducer of pro-inflammatory cytokine expression in human monocytes via phagocytosis that are dependent on both TLR-2 and TLR-4 stimulation (Erride et al., 2007). Biofilm formation takes place by the accumulation of outer membrane proteins (OMPs) (Erride et al., 2006). The biofilm formation involves a variety of pathway that regulates the quorum sensing. Quorum sensing involved in auto inducer production (Smith et al., 2007) control various metabolic process.

The biofilm component endo polysaccharides suppress the activity of neutrophils and contribute to the serum resistance. The expression of various factors {lipid metabolism (CDC, 2004), resistance to antibiotic desiccation & disinfectant as well as protective to the condition of skin, mucus membrane (Jawad et al., 1998 and Wisplinghoff et al., 2007)} accounts for the strains to sustain and colonize the various host environments. The next step after adhesion to epithelial cells is apoptosis of eukaryotic cells (Choi et al., 2008a). This activity is attributed by OmpA, that leads to the metabolic disorder of mitochondria and nucleus and lead to the cell death pathway (Choi et al., 2005 and Choi et al., 2008b) Purified Omp A elicits a Th1-mediated immune response (Lee et al., 2007) via a toll like receptor (TLR)-2-mediated pathway (Kim et al., 2008). Although the pathogenicity factor of Acinetobacter baumannii is in elementary state (not known to provide the diffusible toxin or cytolysin) but few virulence factor have been known e.g. (obtain and utilization of iron resources, hemin utilization system) attribute them to survive in both host and environmental condition (Zimbler et al., 2009 and Dorsey et al., 2003).

NOSOCOMIAL INFECTION:

Acinetobacter baumannii has emerged as an important nosocomial pathogen (Giamarelous, 2006). Although the actual reservoir of Acinetobacter baumannii for nosocomial infection is unknown but the different potential source of hospital setting e.g., hands of staff, ventilators and tubes, soap, gloves etc. and different factors (prion, antibiotic, increase length of hospital stay, poor hygiene of staff etc. the MDR strain of Acinetobacter baumannii usually tends to occur in immunocompromised patients, in patients with serious underlying disease and patients that are usually under the treatment with broad spectrum antibiotics (Celenza et al., 2006)) facilities the colonization and spreading of Acinetobacter baumannii infection.

The rising incidences of MDR A. baumannii usually Carbapanem Resistant Acinetobacter Baumannii infection in hospital setting is significant cause of hospital outbreak. In ICU (Van den Broek, 2006; Marchaim et al., 2007; Saeed et al., 2006) the majority of outbreaks is due to single clone however polyclonal outbreaks have been also reported (Rodriguez-Bano et al., 2004) along with A. baumannii gene spp 3 and gene spp13 TU have also played a significant role in hospital outbreak (Seifert & Gerner-Smidt, 1995 and Lee et al., 2007). At present, different genotyping methods as described before (Abbo, 2005; Go, 1994 and Maslow, 2005) are used to rule out the epidemiological cause of outbreaks.
Figure: 1. Thus infections due to MDR Acinetobacter baumannii are frequently found in ICU where they cause cellulites, respiratory tract infection, central nervous system infection, bacteremia and Urinary Tract Infection (UTI) (Poirel et al., 2003 and Glew et al., 1997)

COMMUNITY ACQUIRED INFECTIONS
An opportunistic pathogen; Acinetobacter baumannii is now recognized as major cause of community acquired infection usually pneumonia. This infection usually become severe to those patients who are under the chronic treatment of chronic obstructive pulmonary disease, diabetes, heavy smokers, excessive alcohol consumer (Falagas et al., 2007). This infections are encountered usually in South East Asia and tropical Australia (Anstey, et al., 2002 and Chen, et al 2001). Unlike, Hospital Acquired Infection caused by MDR Acinetobacter baumannii Community Acquired Infection caused by A. baumannii (Dalhoff and Thomas, 2003) is uncommon.

INFECTION IN WAR AND CAUSALITIES
Recently military and non military person returning from war from Iraq and Afghastain harbor the MDR Acinetobacter baumannii. These MDR strains have been isolated from the deep wound infections; burn patients, wound infection, osteomylities and rarely from the blood samples in case of bacterimnia (CDC, 2004). More recently, it has been known that the acquisition of A. baumannii is due to the contamination of environment of field hospitals and infection transmission in health care facilities (Scott et al., 2007). Infection of MDR is not limited only in conflict but also in natural and manmade disaster such as earthquake that occurred in 1999 in Turkey, the 2002 Bali bombing and military operation. (Oncul et al., 2002 and Davis, 2005)

ANTIBIOTIC RESISTANCE IN ACINETOBACTER
Multidrug resistance isolates of Acinetobacter baumannii have been increasing from the last decades as a cause of numerous global outbreaks as well as an endemic strains in ICU’S. MDR isolates of Acinetobacter baumannii have been reported from hospitals of western countries including Europe, USA, China Korea, Hongkong and Japan as well as from the remote areas such as the South Pacific (Coelho, 2004 and Perez, 2007). Due to this reason at present Acinetobacter baumannii is attracting the attention of entire world owing to its endless capacity to acquire antimicrobial resistance and occurrence of strains that are sensitive to virtually and available drugs (Perez, 2007 and Davis, 2005). The emergence of antimicrobial resistance of Acinetobacter baumannii is due to its capability for genetic exchange. Therefore, Acinetobacter are kept among a unique class of gram negative bacteria that are naturally transformable (Lorenz and Wackernagel, 1994 and Metzgar et al., 2004). An Acinetobacter strain also lacks MutS, so inhibits increased mutations rules (Young and Ornston, 2001). The presence of competence genes COM PECB and COM Q20NM allows the ready uptake of DNA from the Environment (Barbe et al., 2004; Busch et al., 1999 and Herzberg et al., 2000).
Another chromosomal system that is typical in *Acinetobacter baumannii* for the regulation of gene expression is the AdeABC efflux system (Heritier et al., 2006). The gene that encode of Ade ABC system in *Acinetobacter baumannii* produces resistance mutation in the adeS in adeR genes thereby up regulation of AdeABC system to decrease susceptibility to antimicrobial agents (Magnet et al., 2001 and Marchand et al., 2004).

Apart from its intrinsic resistance mainly due to the low permeability of the outer membrane to certain antibiotics as well as constitutive expression of certain efflux pumps, *Acinetobacter baumannii* is also able to acquire and incorporate genetic element such as plasmid transport and integrons (Vila and Pachon, 2008 and Giamarellou et al., 2008). Besides these insertion segments (ISs), it also promotes the gene expression that confer the regulation of resistance to illustrate the presence of Isaba1 element which has been identified in *Acinetobacter baumannii* but not in Enterobacteriaceae or in Pseudomonas aeruginosa, results in over expression of AmpC and OXA-51 IOXA-69 like beta-lactamases and in decreased levels of susceptibility to ceftazidime and carbapenem respectively (Turton et al., 2006 and Herzberg et al., 2000). Genomic sequences analysis of a number of MDR isolates of *Acinetobacter baumannii* revealed the presence of several large genomic islands. (AbaR1, R2, R3 & R5) (Morgan et al., 2009 and Smith et al., 2007) containing MDR gene prompts to be acquired from other gram negative bacteria.

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<tr>
<th>Mode of resistance in <em>Acinetobacter baumannii</em></th>
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<td>Hydrolysis by different ß- lactamase enzyme</td>
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<td>Changes in OMPs and PBPs</td>
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<td>Increased activity of efflux pumps system</td>
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<td>Mutations in different genes(gyrA,parC)</td>
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**MECHANISM OF RESISTANCE OF SELECTED ANTIBIOTICS:**

**B- LACTAM**

ß - lactam antibiotics are the most commonly used antibiotics that are used in the treatment of variety of infectious diseases commonly gram negative and gram positive bacteria (Bartlett, 2003). These agents represents >65% of the world antibiotics market which include penicillin, cephalosporin, carbapenem, monobactam, clavam, penems, OXAcephems (Essack, 2001; Dalhoff, 2006 and Siu, 2002). These agents are characterized by four member ß-lactam ring, fused to a five member sulfur ring system and the cephalosporin where the ß- lactam is fused to sulfur containing ring expanded system and they kill organisms by blocking the crucial trans-peptidation that lead to mechanically strong peptidoglycan through cross linking of peptide strands (Essack, 2001 and Siu, 2002). The resistances to ß-Lactam in *Acinetobacter baumannii* are: hydrolysis by betalactames, changes in PMPs that prevents their action, alteration in the structure of outer membrane protein (OMPs) and other protein including penicillin binding proteins (PBPs) and increased ability of Efflux pumps (Perez, 2007; Van Looveren et al., 2004; Poirel and Nordmann, 2006 and Vila, 2007).

**B-LACTAMASE**

B-Lactamase [EC3.5.2.6] (Abdelhakim et al., 2011) is heterogeneous groups of proteins with structural similarities; composed of α-helices and β-pleated sheets. They is the members of active site serine proteases super family (Knox et al., 2001). This Enzyme was first reported in *E-coli* since then these enzymes are described in gram positive, gram negative and mycobacterium (Livermore, 1995 and Majiduddin, 2002). These enzymes are variably, chromosomally or plasmid encoded often as transposons and integrons (Rowe-Magnus and Mazel, 2002). Four molecular classes of ß-lactamases are known dubbed A-D and it include both metal dependent (Class B) and metal independent (Class A, C, D) enzymes (Majiduddin, 2002 and Helfand, 2003).
1. **Class A β--Lactamases:**

   Class A β-lactamase type of TEM-1 and SHO type as well as PER-1 an ESBL enzyme very prevalent in *Acinetobacter baumannii* strain mostly reported from Turkey, France, Belgium and Bolivia (Celenza et al., 2006; Naas et al., 2006 and Poirel et al., 2005) and VEB1, another ESBL has caused outbreak in French and Belgian hospitals (Naas et al., 2006 and Poirel, 2003). Other class A – beta lactamases like SHIV-12, TEM-92, TEM-116 and Tx-M-2 are reported from different parts of world (Huang et al., 2004 and Endimiani et al., 2007). SCO-1 and GES-11 type of β-lactamases are also reported (Nagano et al., 2004 and Poirel et al., 2007).

2. **Class B β-Lactamases:**

   These enzymes differ from class A and class D carbapenemases by having a metal ion in the active site usually zinc which participates in catalysis (Moubareck et al., 2009 and Walsh, 2005). Five groups of acquired MBL have been identified to date (IMP like ,VIM like ,SIM-1,SPM-1 and GIM-1 enzymes) but only the first three of these groups have been identified in *A.baumannii*. The IMP group consists of currently of 19 variables that divide in seven phylogroup (Walsh, 2005). Six IMP variants belonging to have different phylogroups have been identified in *Acinetobacter baumannii*. Important types of MBL in *Acinetobacter baumannii* are noted from England, Japan, Korea, Hongkong (IMP-1, IMP-2, IMP-4, IMP-5, IMP-6 & IMP-11). In addition VIM-2 type and SIM-1 MBL is reported from Korea (Tognim et al., 2006; Gales et al., 2003 and Yum et al., 2002). Genetic analysis suggests that MB 1 encoding genes are embedded in class -1, integrons structure between 5’ conserved segment 5’CS and 3’ CS together with other antibiotic resistance gene cassettes (Perez et al., 2007).

3. **Class C β-Lactamases:**

   Class C β-lactamases in *Acinetobacter baumannii* are chromosomally encoded by Amp-C gene like other gram negative bacteria. Phylogenetic analysis Amp-C gene suggested that it is closely related to Amp C gene in other bacteria but kept in distinct family of β-lactamases the *Acinetobacter* derived Cephalosporines (ADCs) (Corvec et al., 2003 and Hujer et al., 2005).

4. **Class D β-lactamases:**

   The commonest in *Acinetobacter baumannii* are class D β-lactamases. They are robust penicillinases and some are noted to hydrolyze extended spectrum of cephalosporin’s (Aubert et al., 2001 and Chakravarti et al., 2000). In addition to intrinsic OXA-51 like enzymes, there are three unrelated groups of the carbapenem hydrolyzing oxacillinase has been distinguished. These are OXA -23,OXA-24 and OXA-58 respectively( Perez et al.,2007).They are acquired type carbapenemase .They are chromosomally or plasmid or both acquired. The ubiquitous OXA-51 requires the presence of insertion elements ISAba1 which act as promoter in upper stream of the gene to provide resistance to carbapenem (Heritier et al., 2005 and Turton et al., 2006). OXA-58 type of carbapenem is reported from different parts of world (Giamarellou et al.,2008). In addition OXA-40 and OXA-58 harbouring *Acinetobacter baumannii* are noted from USA outbreaks (Lolans et al., 2006 and Hujer et al., 2006).

**CHANGES IN OMPs AND PBPS:**

The role of OMPs in antibiotics resistance in *A. baumannii* is due to loss of porins (Perez et al., 2007 and Van Looveren et al., 2004). Resistance to meropenem and imipenem in MDR *A.baumannii* clinical isolates is due to loss of heat modifiable 29KDa OMP designated as CarO. This loss is due to the disruption of CaO gene by distinct insertion elements (Mussi et al., 2005).Other resistance mechanism is associated with reduced expression of two proteins (22 and 32KDa) (Bou et al., 2001) and 37-44 and 47 KDa OMPs (Helfand and Bonomo, 2003) One another study made by del Mar Thomas et.al on the outer membrane profile of *A.baumannii* which do not produce carbapenemase enzymes but resistance to carbapenem revealed that loss of 31 to 36 KDa OMPs. Similarly, loss of 43 Kda proteins homologous to the OPrD of *Pseudomonas aeruginosa* involved in the carbapenem resistance has implicated in β-lactam resistance in *A. baumannii*. *A.baumannii* isolates express normally an OPrD like proteins.
A study suggested that reduced expression of PBP2 as described isolates from Seville (Spain) is responsible for the carbapenem resistance in *A. baumannii* (Bou *et al.*, 2001) but another study made by Getustein *et al.* (Gehrlein *et al.*, 1991) showed that resistance mutant of *A. baumannii* in vitro has hyper produced a 24 Kda PBP and also produced six others PBPs at lower level. Other similar study was done by Fernandez Cuenca, *et al.* to describe the relationship mechanism between β-lactamase production, OMP and PBPs profile on the variable β-lactam resistance profile (Fernandez-Cuenca *et al.*, 2003).

**EFFLUX PUMPS SYSTEM:**
In Acinetobacter *baumannii* an AdeABC efflux system has been characterized belonging to the resistance nodulation division (RND) family of the efflux system (Poole, 2004 and Magnet *et al.*, 2001). This efflux system pumps almost all classes of antibiotics including amino glycosides, cefataxime, tetracycline, erythromycin, chloramphenicol, trimethoprim and florquinoxolones (Poole, 2004 and Magnet *et al.*, 2001). The carbapenem resistance in *A. baumannii* results from the over expression of AdeABC efflux pump system. This mechanism needs the conjugation of carbapenem hydrolyzing oxacillinase (Heritier *et al.*, 2005). Further studies has identified that the expression of this efflux system has been contracted by two regulator (adeR) and sensor (adeS) system. This regulation encoded by adeST gene i.e located at the upstream of Ade ABC efflux gene (Marchand *et al.*, 2004). More, recently multidrug pumps system AbeM that belongs to MATE (Multidrug and Toxic compound Extrusion) has been characterized which usually pumps fluoroquinolones (Su *et al.*, 2005). The most recent efflux system identified as AbeS belonging to small multidrug resistance family of bacterial integral membrane proteins (BIMP). It’s substrate for pump is mainly quinolones, macrolides and chloramphenicols (Srinivasan *et al.*, 2009).

**RESISTANCE TO AMINOGLYCOSES:**
Besides, AdeABC multidrug efflux pumps system resistance to amino glycosides in other bacteria; in *A. baumannii*, there is extra system for resistance to aminoglycosides called as amino glycosides modifying enzymes (AMEs). These enzymes include amino glycosides, phosphotransferase, and aminoglycosides acetyl transferase and aminoglycosides nucleotidyltransferase (Nmec *et al.*, 2004 and Van Looveren *et al.*, 2004). More recently a new type of AME encoded by aac (6’)-Iad has been identified in Japan (Doi *et al.*, 2004) which mainly is related to amikacin resistance.

**RESISTANCE TO QUINOLONES**
In addition to the AdeABC efflux system, modification in the structure of quinolones resistance determining regions of gyrA and parC gene is responsible for the quinolones resistance in *A. baumannii*. This modification is caused by mutation (Vila *et al.*, 1995 and Vila *et al.*, 1997). However, unlike in enterobacteriacea plasmid mediated quinolones resistance gene *qnrA* has not yet been identified in *A. baumannii* isolates (Robicsek *et al.*, 2005).

**RESISTANCE TO TETRACTYCLINE**
Resistance to tetracycline till date are concerns with two different mechanism in *A. baumannii* tetA and tetB are specific transposon mediated efflux pumps whereas other system is ribosomal protection proteins that shields the ribosome. This ribosomal protection proteins is the protein encoded by tet M gene and this protect mainly ribosome from tetracycline, coxyccycline and minocycline (Moore *et al.*, 2005) Tigecycline, a first glycoxycline and substrate for plasmid borne flavin-dependent monooxygenase, this has not yet been detected in *A. baumannii* (Ruzin *et al.*, 2007), however the role of AdeABC efflux pump is resistance to tigecycline is described by Ruzin *et al.* (Ruzin *et al.*, 2007).

**RESISTANCE TO POLYMIXIN**
Although resistance to polymixin is still considered to be rare but with the increase in use of polymixin resistance to colistin is becoming common and more widespread (Gales *et al.*, 2001). The core mechanism of resistance to colistin lies in the modification of lipopolysaccharide of *A. baumannii* (Perez *et al.*, 2007) now, the report of resistance to colistin in *A. baumannii* is described by A.O Reis *et al.* and A.C. Gates *et al.* (Reis *et al.*, 2003 and Li *et al.*, 2006). Heteroresistance in *A. baumannii* to colistin is another great alarm to the prevent world is described by Yau *et al.* (Yau *et al.*, 2009) and Hawley, *et al.* (Hawley *et al.*, 2008) as the colistin is the last resort of treatment to the infection caused by MDR Acinetobacter *baumannii* (Perez *et al.*, 2007).
OPTIONS OF TREATMENT
MDR isolates of Acinetobacter baumannii are increasing worldwide and constitute alarming events for emerging drug resistance (Dio et al., 2009 and KO et al., 2009). Carbapenem, which are considered as gold standard for the treatment of MDR but found resistance to MDR A.baumannii (Vandenbergh MFQ et al., 2005) resulting in global threat to the current antimicrobial world. It is therefore vital that therapeutic strategies optimize the use of existing antimicrobial agents and minimize the possibilities for the evaluation of drug resistance. Different approaches for the treatment of A.baumannii infections have been considered in details in several recent review (Gilad and Carmeli, 2008 and Dijkshoorn et al., 2007). Tables below list the classes of antimicrobial agents that are currently considered to have potentials activity against A.baumannii.

Table1: Antibiotic having potent activity against Acinetobacter baumannii

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<tr>
<th>Polymyixns</th>
<th>Carbapenem</th>
<th>Sulbactams</th>
<th>Tigecycline</th>
<th>Peptides</th>
<th>Fluroquinolones</th>
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POLYMIXIN
Polymixins are discovered in 1945 and were abandoned from the clinical use till 1980’s except for the treatments of patients with cystic fibrosis. (Giamarellou et al., 2008 and Karageorgopoulos et al., 2008) and they are the cationic polypeptides that has mode of action in the both outer and cytoplasmic membrane usually in the lipopolysaccharide layers of gram negative bacteria (Karageorgopoulos et al., 2008). There are five chemically different compounds of polymixin, A-E. Amongst them, polymixin B and ploymyxin E are suitable for clinical use. The emergence of MDR gram negative bacilli had lead to the survival of polymixin especially colistin. Colistin is identical to polymixin E and are available in two forms colistin sulfate and colistinmethate sodium (CMS) (Giamarellous, 2006 and Ioannis et al., 2010). CMS has inferior antibacterial activity and lower toxicity so it is administered parenterly(Giamarellous ,2006 and Ioannis et al.,2010).

Colistin is used for the treatment of bacteremia, orthopedic device infection, osteomyelitis, central nervous system infection, wound and urinary tract infection (Gerner-Smidt et al., 1991; Karageorgopoulos et al., 2008 and Kasiakou et al., 2005). Although initially, the use of colistin in clinical use was limited due to misconception of highly toxicity to kidney and nervous system but a number of report suggested in modern use of colistin has not been associated with significant neurotoxicity although nephrotoxicity remains a concern (Linden and Paterson, 2006 and Garnacho-Montero et al., 2003). CMS has been administrated intravenously, intramuscularly, intrathecially or by inhalation (in neublized form) especially for the treatment of pneumonia caused by MDR A.baumannii to overcome the limited penetration of systematic colistin into luns (Giamarellous, 2006). Different concentrations of CMS are used in different country depending upon the status of patients (Michalopoulos et al., 2008 and Falagas ME et al., 2006). Polymixin show bactericidal activity against A.baumannii and resistance of A.baumannii against polymixin is still extremely rare (Li et al 2003). Perhaps, surprisingly reports of high rate of resistance to colistin have been recently been reported in A.baumannii isolates from two Korean hospitals (Ko et al., 2007). Increasing use of polymixin had lead to colistin resistance, particularly heteroresistance (Hawley JS et al., 2008 and Ko et al., 2007). Clinical use of polymixin against A.baumannii isolates has proven to be extremely successful. Different retroprospective reported up to 87% cure (Falagas et al., 2010; Kallel et al., 2007 and Matteo Bassetti et al., 2008).
Polymixin have been tested extensively in combination regimes with others agents to treat MDR *A. baumannii*. Among these combination colistin and carbapenem combination showed superior result which is supported by the study done by Falags, et al (Falagas et al., 2010) Various study have been done to determine the efficacy of colistin when given through various route of administration. The first study on the clinical use of intravenous colistin for the treatment of infection caused by MDR *A. baumannii* on *P. aeruginosa* noted favorable clinical outcomes (Diamantis et al., 2010). Further studies assessed prospectively or retroprospectively treatments with colistin VAP caused by *A. baumannii* or *P. aeruginosa* (Jason et al., 2007 and Ray et al., 2007) and noted almost no difference between the monotherapy of colistin and treatment with other agents (carbapenem). Similarly, in some of the few relevant cases reported in the literature administration of nebulised colistin as the sole of treatment against *A. baumannii* nosocomial pneumonia (Kwa et al., 2005), nosocomial meningitis (Falagas et al., 2007) showed the favorable response.

**CARBAPENEM**

Carbapenem (especially meropenem and Imipenem) have been reerrated as the choice of drugs for the treatment of infections caused by *A. baumannii* for the past decade (Bergogne -Berezin et al., 1996 and Van Looveren et al., 2004). However, several recent reports suggesting the clinical isolates of *A. baumannii* resistance to carbapenem reaching the level of nearly 90% or ≥90% in some countries (Van Looveren et al., 2004; Gales et al., 2006 and Karageorgopoulos et al., 2008). In the surveillance study, resistance rate of *A. baumannii* to carbapenem was found to be nearly 40% and 30% in Latin America and the Asia Pacific region respectively. This is higher in comparison to those Europe and North America (nearly 15%, 12% respectively) (Reiner et al., 2007). To overcome the increasing trend of carbapenem resistance *A. baumannii* worldwide, now at present various combination of carbapenem with other agents such as sulbactum, tobramycin, amikacin, colistin, rifampicin and azetronem is being assessed both in vivo and vitro (Karageorgopoulos et al., 2008).

**SULBACTUM**

Sulbactum, β-lactamase inhibitors represents active bactericidal or bacteriostatic agents. *A. baumannii* by binding to its penicillin binding protein (Tripodi et al., 2007 and Rafailidis et al., 2007). At present sulbactum used successfully for the treatment of MDR *A. baumannii* infections such as VAP (ventilator Associated pneumonia), meningitis, catheter related bacteremia, (Paul et al., 2004) respiratory tract and UTI (Smolyakov et al., 2003). In most cases, sulbactum has been used in combination with Ampicillin in the ratio 2:1 (Fernandez-Cuenca et al., 2004). However, efficacy for enhanced antimicrobial activity seems to be insignificant by use of combination of sulbactum with ampicillin cefoterazone or antipseudomonal penicillin (Rafailidis et al., 2007). At the mean time the combination of sulbactum with carabapenem (especially imipenem) have shown effective results in the treatment of CRAB (Carbapenem Resistant Actinobacter baumannii) (Lee et al., 2007 and Ko et al., 2004). Besides, the outcomes of triple combination of β-lactam (Imipenem, ticracillin, ticracillin/calvulanic acid and rifampicin) plus sulbactum and rifampicin results in enhanced survival in mouse pneumonia model caused by two different isolates of *A. baumannii* (Wolf et al., 1999). Although sulbactum containing compounds is considered a safe and effective therapeutic option against *A. baumannii* isolates but the trend of use of this compounds has declared significantly due to the development and spread of new mechanism of resistance (Higgins et al., 2004 and Karageorgopoulos et al., 2008).

**TIGECYCLINE**

Tigecycline, a semisynthetic derivative of minocycline, belonging to a novel class of antimicrobial agents, Glycyclines have been used in therapy for infection caused by MDR *A. baumannii* (Livermore, 2005 and Karageorgopoulos et al., 2008). The mode of action of tigecycline is bacteriostatics, similar to the tetracyclines (Song et al., 2007). Tigecycline is now successful in treatment of septic shock due to PAN resistance *A. baumannii* infection caused by minocycline resistant, Multidrug resistant, imipenem resistant isolates colistin resistant (Scheetz et al., 2007; Halstead et al., 2007 and Taccone et al., 2005). In constrasts a recent report describes that tigecycline may not be consistently active against the imipenem resistant isolates (Karageoropoulos et al., 2008). Furthermore, occurance of MDR *A. baumannii* infection with high tigecycline resistance is noted from patients receiving tigecycline for the treatment (Navon-Venezia et al., 2007).
Other report include blood stream infection caused by non-susceptible *A. baumannii* in patient's receiving tigecycline (Peleg et al., 2007a). In vitro analysis have revealed that resistance to tigecycline is mediated by the over expression of multidrug efflux pump and emergence of resistance to strains to tigecycline during the therapy (Peleg et al., 2007b and Gordon and Wareham, 2009). In addition super infections with pathogens inherently resistance to tigecycline (*P. aeruginosa*, *Proteus spp.*, *Providencia spp.*) are the matter of concerns. Poulaleou, et al reported that amongst 45 patients treated with tigecycline for MDR or PDR infection 10 episodes of super infections by inherently resistance pathogens (Van Looveren and Goossens, 2004 and Lee et al., 2004)

### Others Antibiotics:

Others antibiotics that have potent activity against MDR *A. baumannii* is discussed elsewhere (Karageorgopoulos et al., 2008 and Neonakis et al., 2010) and include following agents.

<table>
<thead>
<tr>
<th>Antibiotic groups</th>
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<tr>
<td>Aminoglycosides</td>
<td>Amikacin (Halstead et al., 2007) Tobramycin (Rodriguez Guardado et al., 2008)</td>
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<tr>
<td>Flulorquinolones</td>
<td>Ciprofloxacin (Scheetz et al., 2007) Levofloxacin (Joly-guillou et al., 2000)</td>
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<tr>
<td>Rifampin</td>
<td>Rifampicin (Betrosian et al., 2008 and Giamarellos-Bourboulis et al., 2001)</td>
</tr>
<tr>
<td>Peptides</td>
<td>Alyteserine-1C and its [E4K] analogue, Buforin II, Human β-defensin 2 [hBD2] (Neonakis et al., 2010)</td>
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</table>

### Combination Therapy

Besides, Effective treatment with monotherapy and lack of new treatments various strategies such as dual or triple antimicrobial therapy are used to combat with MDR *Acinetobacter baumannii*. A considerable number of in vitro studies and animal studies using a mouse model of pneumonia have been carried out to analyze the synergistic effect of the combined drugs (Principle et al., 2009 and Pantopoulou et al., 2007). Various combinations include carbapenem with amikacin, colistin, tobramycin, rifampicin, sulbactum and azteronam (Karageorgopoulos et al., 2008). Others include colistin with rifampicin, monocyclin, ceftazidime (Ko et al., 2004). Furthermore tigecycline with amikacin, levofloxacin, colistin and imipenem has been recommended for the treatment of MDR *Acinetobacter baumannii* (Principle et al., 2009). Though combination therapy may provide mixed results in vitro, non synergistic result (Karageorgopoulos et al., 2008 and Scheetz et al., 2007) synergistic result (Song et al., 2007 and Sader et al., 2005). However, the best combination regimes may be chosen by clinician to achieve the synergistic activity for treatment of patients associated with MDR *A. baumannii* infections. More recently, new antimicrobial that have been expected to show the activity of against the MDR *A. baumannii* (lactoferrin derived peptide hlf (1-11)) has been studied in animal model (Dijkshoorn et al., 2004).

### CONCLUSION

It is concluded that *Acinetobacter baumannii* is the top ranked predominated organism associated with nosocomial infection and several out breaks worldwide. Emergence of MDR strains is now one of concerns to clinician in treating infection due to *Acinetobacter baumannii* in which sulbactum, tigecycline polymixin, carbapenem are currently recommended for empirical treatment. Concomitant search for alternative newer drugs should be continued because, although newer antimicrobial drugs offer hope for treatment of infection caused by *Acinetobacter baumannii*, emergence of resistant to new drugs is also not so far in the future. Therefore, generating an effective vaccine or phage therapy or novel therapeutic agents offer the ultimate solution of the problem. Thus, this review highlights the urgent need of research addressing key issues in the treatment of MDR *Acinetobacter baumannii* infections, to check the outbreaks (endemic, epidemic, sporadic), furthermore, there is need of intense study of problems and genomic of *Acinetobacter baumannii* to understands the mechanism of resistance and to check it.
REFERENCES


Buddha et al


Buddha et al


