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Review article

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

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ABSTRACT: Infections due to Mutli Drug Resistant *A. baumannii* (MDRAB) is now recognized as a major public health problem worldwide. The nosocomial infection due to MDRAB 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 *A. 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*, β-lactamase, Carbapenem,, infections, multidrug-resistance

INTRODUCTION

The emergence of MDRAB is the major cause of nosocomial Infection associated with a significant morbidity and mortality (Joly-Guillou, 2005 and Perez *et al*., 2007). Currently, Mutli drug Resistant (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 MDRAB.

HISTORY

*Acinetobacte*r 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.*

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In the early 20th century taxonomic history of *Acinetobacter* species have been assigned in family Neisseriaceae with genera *Neisseria, Kingnella and 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 *A. 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 Constatintiniu, et al (Sofia Constatintiniu et al., 2004). In clinical setting *A. 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 and 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, MDRAB has emerged as significant problem worldwide (Gould, 2008). There are some reports that describe the MDRAB as challenge to the modern era from Europe, North America, South America, South Pacific Asia and Australia (Perez et al., 2007; Van Looveren, 2004; Lee, 2004 and Van Dessel, 2004). The rising evidence of MDRAB 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 MDRAB 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 *A. baumannii* along with geno species 3 and genospecies 13TU are the most frequently found species in human clinical specimen (Tjernberg. and Ursing, 1989; Gerner-Smidt andTjernberg, 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 *A. baumannii;* gen.sp.3 and gen.sp.13TU are present in vegetable, food, arthropods, meat, soil, water and rice (Huys et al .,2007a; Huys et al., 2007b; Fournie and Richet, 2006 and Raoult , 2004).

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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 *A. baumannii* with significant role in pathogenicity that have yet to be assessed in mammalian model (Smith et al., 2007).

ACINETOBACTER BAUMANNI INFECTION

The initial step in the colonization, infection and epidemic spread of *A. baumanni* 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 pilli 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 and 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 OmpA elicits a Th_1-mediated immune response (Lee et al., 2007) via a toll like receptor (TLR)-2-mediated pathway (Kim et al.,2008).

Although the pathogencity factor of *A. 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:

A. baumannii has emerged as an important nosocomial pathogen (Giamarellous, 2006). Although the actual reservoir of *A. 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 *A. baumannii* usually tends to occur in immune compromised 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 *A. baumannii* infection. The rising incidences of MDRAB usually Carbapenem Resistant *A. 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 andGerner-Smitdt, 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.

INFECTION IN WAR AND CAUSALITIES

Recently military and non military person returning from war from Iraq and Afghastain harbor the MDRAB. 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 bacterimia (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)

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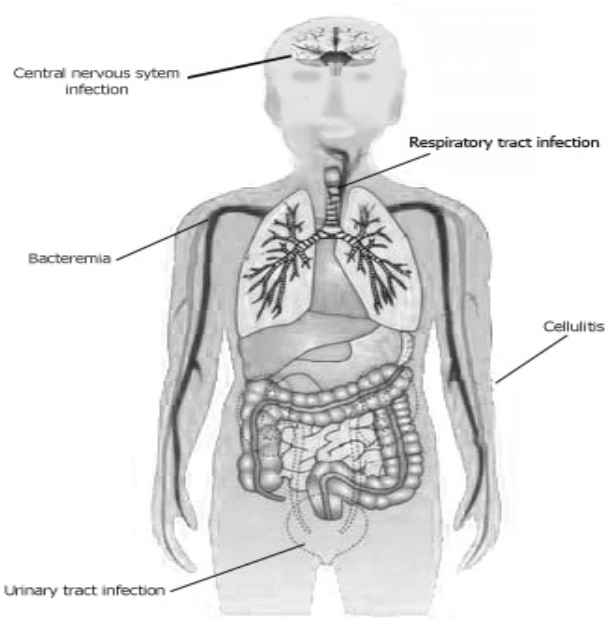

Figure: 1: The infections due to MDR Acinetobacter baumannii are frequently found in ICU where they cause cellulites, respiratory tract infection, central nervous system infection, bacteremia and Urinary Tract Infection (UTI) (Poirel et al., 2003 and Glew et al., 1997)

ANTIBIOTIC RESISTANCE IN ACINETOBACTER

Multidrug resistance isolates of *A. baumannii* have been increasing from the last decades as a cause of numerous global outbreaks as well as an endemic strains in ICU'S. MDRAB 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 *A. 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 *A. 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 *A. baumannii* for the regulation of gene expression is AdeABC efflux system (Heritier et al., 2006). The gene that encode of AdeABC system in *A. 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, *A. 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 *A. 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).

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Genomic sequences analysis of a number of MDR isolates of *A. baumannii* revealed the presence of several large genomic islands. (AbaR1, R2, R3 and R5) (Morgan et al., 2009 and Smith et al., 2007) containing MDR gene prompts to be acquired from other gram negative bacteria. Table 1.

Table 1: Mode of resistance in *Acinetobacter baumannii*

Hydrolysis by different β- lactamase enzyme
Changes in OMPs and PBPs
Increased activity of efflux pumps system
Mutations in different genes(gyrA,parC)

MECHANISM OF RESISTANCE OF SELECTED ANTIBIOTICS:

β - LACTAM:

β - 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 β-lactam ring, fused to a five member sulfur ring system and the cephalosporin where the β- 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 β-Lactam in *A. 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).

β -LACTAMASE:

β -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 are 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 β-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 *A. 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 form 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).

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Six IMP variants belonging to have different phytogroups have been identified in *A. baumannii*.Important types of MBL in *A. baumannii* are noted from England, Japan, Korea, Hongkong (IMP-1, IMP-2, IMP-4, IMP-5, IMP-6 and 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 l 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 *A. 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 of 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 *A. 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 oxacillnase 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-23, OXA-58 type of carbapenem is reported from different parts of world(Giamarellou et al., 2008). In addition OXA-40 and OXA-58 harbouring *A. 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 MDRAB 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 33KDa) (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 *A. 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 florquinolones (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.

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This regulation encoded by *adeST* gene i.e. located at the upstream of adeABC efflux gene (Marchand et al., 2004). More, recently multidrug pumps system AbeM that belongs to MATE (Multidrug and Toxic compound Extrution) has been characterized which usually pumps fluroqunolones (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 AMINOGLYCOSIDES

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 enterobacteriaceae plasmid mediated quinolones resistance gene *qnrA* has not yet been identified in *A. baumannii* isolates (Robicsek et al., 2005).

RESISTANCE TO TETRACYCLINE

Resistance to tetracycline till to 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 tetM gene and this protect mainly ribosome from tetracycline, coxycycline and minocycline (Moore et al., 2005) Tigecycline, a first glycocycline 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 POLYMYXIN

Although resistance to polymyxin is still considered to be rare but with the increase in use of polymyxin 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 MDRAB (Perez et al., 2007).

OPTIONS OF TREATMENT

MDR isolates of *A. 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 MDRAB (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 reviews (Gilad and Carmeli, 2008 and Dijkshroorn *et al*., 2007). Tables below list the classes of antimicrobial agents that are currently considered to have potentials activity against *A. baumannii.*

POLYMYXIN

Polymyxins 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).

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There are five chemically different compounds of polymyxin, A-E. Amongst them, polymyxin B and ploymyxin E are suitable for clinical use. The emergence of MDR gram negative bacilli had lead to the survival of polymyxin especially colistin .Colistin is identical to polymyxin 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).

Table2: Antibiotic having potent activity against *A. baumannii*

Polymyxins
Carbapenem
Sulbactams
Tigecycline
Peptides
Fluoroquinolones

Colistin is used for the treatment of bacteremia, orthopedic device infection, osteomyletis, 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 MDRAB to overcome the limited penetration of systematic colistin into lungs (Giamarellous, 2006). Different concentrations of CMS are used in different country depending upon the status of patients (Michalopoulos et al., 2008 and Falagas et al., 2006). Polymyxin show bactericidal activity against *A. baumannii* and resistance of *A. baumannii* against polymyxin 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 polymyxin had lead to colistin resistance, particularly heteroresistance (Hawley et al., 2008 and Ko et al., 2007). Clinical use of polymyxin 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). Polymyxin have been tested extensively in combination regimes with others agents to treat MDRAB. 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 MDRAB on *P. aeruginosa* noted favorable clinical outcomes (Diamantis et al., 2010). Further studies assessed prospectively or retroprosepectively 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 relevalent cases reported in the literature administration of neubulised 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 regarded 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 MDRAB infections such as VAP (ventilator Associated pneumonia), megnintitis, 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 *A. 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 MDRAB (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 constracts a recent report describes that tigecycline may not be consistently active against the imipenem resistant isolates (Karageorpoulos et al., 2008). Furthermore, occurrence of MDRAB infection with high tigecycline resistance is noted from patients receiving tigecycline for the treatment (Navon-Venezia *et al*., 2007).

Other reports include blood stream infection infection caused by non-susceptible *A. baumannii* in patients 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 MDRAB is discussed elsewhere (Karageorgopoulos *et al*., 2008 and Neonakis *et al*., 2010) and include following agents.

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

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 MDRAB. 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, levofloxicin, colistin and imipenem has been recommended for the treatment of MDRAB (Principle et al., 2009). Though combination therapy may provide mixed results invitro, non synergistic result (Karageorpoulos 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 clician to achieve the synergistic activity for treatment of patients associated with MDRAB infections. More recently, new antimicrobial that have been expected to show the activity of against the MDRAB (lactoferrin derived peptide hIf (1-11)) has been studied in animal model (Dijkshoorn *et al*., 2004).

CONCLUSION

It is concluded that *A. 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, tigeyciline polymyxin, 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 *A. 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 MDRAB infections, to check the outbreaks (endemic, epidemic, sporadic), furthermore, there is need of intense study of problems and genomic of *A. baumannii* to understands the mechanism of resistance and to check it.

REFERENCES

Abbo A, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, and Carmeli Y (2005). Multidrug resistant *A. baumannii*. Emerg Infect. 11: 22-29.

Abdelhakim A, Yamina M, Mohammed SS, Hala MA, Mervat GEl-A, Souhila A, and Rabah B (2011). Resistance to β-lactams of human and veterinary *Salmonella* isolates in Egypt and Algeria. African Journal of Microbiology Research. 5: 802-808.

Anstey NM, *et* al., (2002). Community acquired bacteremic *Acinetobacter* pneumonia in tropical Australia is caused by the diverse strains of *Acinetobacter bauamnnii*, with carriage in the throat in at risk groups. J Clin Microbiol. 40: 685-686.

Aubert D, Poirel L, Chevalier J, Leotard S, Pages JM, and Nordmann P (2001). Oxacillinase mediated resistance to cefepime and susceptibility to ceftazidime in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 48: 1615-1620.

Ayan M, Durmaz R, Aktas E, and Durmaz B (2003). Bacteriological, clinical and epidemiological characteristic of Hospital-acquired *A. baumannii* infection in a teaching hospital. J Hosp Infect. 54: 39-45.

Barbe V, Vallenet D, Fonknechten N, Kreimeyer A, Oztas S, Labarre L, Cruveiller S, Robert C, Dupart S, Wincker P, Ornston LN, Weissenbach J, Marliere P, Cohen GN, and Medigue C (2004). Unique features revealed by the genome sequence of *Acinetobacter spp.* ADP1, a versatile and naturally transformation competent bacterium. Nucleic Acids Res. 32: 5766-5779.

Bartlett JG (2003-2004). Pocket Book of Infectious Disease Therapy. Lipincoot Williams and Wilkins, Baltimore.

Bassetti M, Righi A, Esposito E, Petrosillo N, Nicolini L (2008). Drug Treatment for Multidrug-resistant *A. baumannii* Infections. Future Microbiology. 3(6): 649-660.

Bergogne -Berezin E and Towner KJ (1996). *Acinetobacter spp* as nosocomial pathogens: Microbiological, clinical, and epidemiology features. Clin Microbiol Rev. 9: 148-165.

Berlau J, Aucken H, Malnick H and Pitt, T (1999). Distribution of *Acinetobacter species* on skin of healthy humans. Eur J Clin Microbiol Infect Dis. 18: 179-183.

Boerlin P, Eugster S, Gaschen F, Straub R and Schawalder P (2001). Transmission of opportunistic pathogens in a veterinary teaching hospital.Vet Microbiol. 82: 347-359.

Bou G, Cerverco G, Domingeuz MA, Quereda C, Martinez-Beltran J (2001). Characterization of a noscomial outbreak caused by a multiresistant *A. baumannii* strain with a carbapenem hydrolyzing enzyme: high level carbapenem resistant in *A. baumannii* is not due solely to the presence of β-lactamase. J. Clin Microbiol. 38: 3299-3305.

Busch S, Rosenplanter C and Averhoff B (1999). Identification and characterization of ComE and ComF, two novel pilin-like competence factors involved in natural transformation of *Acinetobacter sp*. Strain BD413.Appl. Environ. Microbiol. 65: 4568-4574.

Celenza G, Pellegrini C, Caccamo M, Segatore B, Amicosante G, Perilli M (2006). Spread of *bla* $_{\text{CTX-M-type}}$ and *bla* $_{\text{PER-2}}$ β-lactamase genes in clinical isolates from Bolivian hospitals. J Antimicrob Chemother. 57: 975-978.

Centers for Disease Control and Prevention (2004). *A. baumannii* infections among patients at military medical facilities treating injured US service members, 2002-2004. Morb Mortal Wkly Rep. 53: 1063-1066,

Chakravarti DN, Fiske MJ, Fletcher LD and Zagursky RJ (2000). Application of genomics and proteomics for the identification of bacterial gene products as potential vaccine candidates. Vaccine. 19: 601-612.

Chen MZ, *et al*., (2001). Severe community acquired pneumonia due to *A. baumannii*. Chest. 120: 1072-1077.

Choi CH, Hyun SH, Lee JY, Lee JS, Lee YS, Kim SA, *et al*., (2008b). *A. baumannii* outer membrane protein A targets the nucleus and induces cytotoxicity. Cell Microbiol. 10: 309-319.

Choi CH, Lee EY, Lee YC, Park TI, Kim SA, *et a*l., (2005). Outer membrane protein 38 of *A. baumannii* localizes to the michodria and induces apotosis of epithelial cells. Cell Microbiol. 7: 1127-1138.

Choi CH, Lee JS, Lee YC, Park TI, Lee JC (2008a). *A. baumannii* epithelial cells and outer membrane protein A mediates interaction with epithelial cells. BMC Microbiol, 8: 216.

Coelho J, Woodford N, Turton J, Livermore DM (2004). Multi-resistant acinetobacter in the UK: how big a threat? Hosp Infect. 58: 167-169.

Corvec S, Caroff N, Espaze E, Giraudeau C, Drugeon H, Reynaud A (2003). AmpC cephalosporinase hyper production in *A. baumannii* clinical strains. J Antimicrob Chemother. 52: 629-635.

Dalhoff A and Thomas CJ (2003). The art of fusion: from penams and cephems to penems. Chemotherapy. 49:105-120.

Dalhoff A, Janjic N, Echols R (2006). "Redefining penems". Biochemical Pharmacology 71 (7): 1085–1095.

Davis KA, Moran KA, McAllister CK and Gray PJ (2005). Multidrug-resistant *Acinetobacter* extremity infections in soldiers. Emerg Infect Dis. 11: 1218-1224.

del Mar Tomas M, Cartelle M, Pertega S, *et al*., (2005). Hospital outbreak caused by carbapenem resistant strains of *A. baumannii*: patient's prognosis and risk factors for colonosation and infection. Clin Microbial Infect. 11: 540-546.

Denton M, Wilcox MH, Parnell P, *et al*., (2005). Role of environmental cleaning in controlling an outbreak of *A. baumannii* on a neurosurgical intensive care unit. Intensive crit care Nurs. 21: 94-98.

Diamantis P, Kofteridis, *et al*., (2010). Aerosolized plus Intravenous Colistin versus Intravenous Colistin Alone for the Treatment of Ventilator-Associated Pneumonia: A Matched Case-Control Study. Clinical Infectious Diseases. 51: 1238-1244.

Dijkshoom L and Nemec A (2008). The diversity of genus Acinetobacter. In: Gerischer U, editor.*Acinetobacter* molecular biology. Norfolk: Caister Acedemic Press. P. 1-34.

Dijkshoorn L, *et al*., (2004). The synthetic N-terminal peptide of human lactoferrin, hLF (1-11), is highly effective against experimental infection caused by multidrug-resistant *A. baumannii.* Antimicrob Agents Chemother. 48: 4919-4929.

Dijkshroorn L, Nemec A, Seifert H (2007). An increasing threat in hospitals: multidrug resistant *A. baumannii*. Nat Rev Microbiol. 5: 939-951.

Dio Y, Husain S, Potoski BA, McCurry KR, Paterson DL (2009). Extensively drug resistance *A. baumannii*. Emerg Infect Dis. 15: 980-982.

Doi Y, Wachino J, Yamane K, Shibata N, Yagi T, Shibayama K, Kato H and Arakawa Y (2004). Spread of novel aminoglycosides resistance gene *aac* (6')-lad among *Acinetobacter* clinical isolates in Japan. Antimicrob Agents Chemother. 48: 2075-2080.

Dorsey CW, Beglin MS, Actis LA (2003). Detection and analysis of iron uptake components expressed by *A. baumannii* clinical isolates. J Clin Microbiol. 41: 4188-4193.

Endimiani A, Luzzaro F, Migliavacca R, Mantengoli E, Hujer AM, Hujer KM, Pagani L, Bonomo RA, Rossolini GM and Toniolo A (2007). Spread in an itlaian hospital of a clonal *A. baumannii* strain producing the TEM-92 extended spectrum β-lactamase. Antimicrob Agents Chemother. 51: 2211-2214.

Essack SY (2001). The development of β-lactamase. Pharm Res. 18: 1391-1399.

Falagas ME, Bliziotis JA, Tam VH (2007). Intraventicular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence. Int J Antimicrob Agents. 29: 9-25.

Falagas ME, Karveli EA, Kelesidis I, Kelesidis T (2007). Community-acquired acinetobacter infections. Eur J Clin Microbiol Infect Dis. 26: 857-868.

Falagas ME, Kasiakou SK, Kofteridis DP, Roditakis G, Samonis G (2006). Effectiveness and nephrotoxicity of intravenous colistin for treatment of patients with infections due to polymyxin -only-susceptibility(POS) Gram negative bacteria.Eur J Clin Microbiol Infect Dis. 25: 596-599.

Falagas ME, Rafailidis PI, Ioannidou E, Alexious VG, Matthaiou DK, Karageogopoulos DE, *et al*., (2010). Colistin therapy for microbiologically documented multidrug resistant Gram -negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents. 35: 194-199.

Fernandez- Cuenca F, Pascula A, Vila J, Bou G, Cisneros JM, *et al*., (2004). Clonal diversity and antimicrobial susceptibility of *A. baumannii* isolated in spain.A nationwide multicenter study: GEIH-Ab project (2000). Enferm Infect Microbiol Clin. 22: 267-271.

Fernandez-Cuenca F, Martinez-Martinez L, Conejo MC, Ayala JA, Perea EJ, Pascual A (2003). Relationship between β-lactamase production, outer membrane protein and penicillin proteins on the activity of carbapenem against clinical isolates of *A. baumannii*. J Antimicrob Chemother. 51: 565-574.

Fournie PE, Richet H (2006). The epidemiology and control of *A. baumannii* in health care facilities. *Clin Infect Dis.* 42*:* 692-699.

Gales AC, Jones RN, Sader HS (2006). Global assessment of the antimicrobial activity of polymyxin B against S4 731 clinical isolates of Gram negative bacilli: report from the SENTRY antimicrobial surveillance programme (2001-2004). Clin Microbial Infect. 12: 315-321.

Gales AC, Rei AO and Jones RN (2001). Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretive criteria and quality control guidelines. J. Clin Microbiol. 39: 183-190.

Gales AC, Tognim MC, Resi AO, Jones RN, Sader HS (2003). Emergence of an IMP -like metallo enzyme in an *A. baumannii* clinical strain from a Brazilian teaching hospital. Diagn Microbiol Infect Dis. 45: 77-79.

Garnacho-Montero J, *et al*., (2003). Treatment of multidrug-resistant *A. baumannii* ventilator -associated pneumonia (VAP) with intravenous colistin: a comparision with imipenem -susceptibility VAP. Clin Infect Dis. 36: 1111-1118.

Gehrlein M, Leying H, Cullman W, Wendt S, Opferkuch W (1991). Imipenem resistance in *A. baumannii* is due to altered penicillin-binding proteins. Chemotherapy. 37: 405-412.

Gerner-Smidt P, Tjernberg I and Ursing J (1991). Reliability of phenotypic tests for identification of Acinetobacter species. J.Clin.Microbiol. 29: 277-282.

Giamarellos-Bourboulis EJ, Xirouchaki E, Giamarellous H (2001). Intractions of colistin and rifampin on multidrug -resistant *A. baumannii*. Diagn Microbiol Infect Dis. 40: 117-120.

Giamarellou H, Antoniadou A, Kanellakopoulou K (2008). *A. baumannii*: a universal threat to public health? Int Journal of Antimicrob Agents. 32: 106-119.

Giamarellous H, Treatment for multidrug-resistant bacteria. Expert Rev Anti Infect Ther (2006). 4: 601-618.

Gilad J, Carmeli Y (2008). Treatment options for multidrug-resistant *Acinetobacter species*. Drugs. 68: 165-189.

Glew RH, Moellering RC, Kunz LJ (1997). Infection with *Acinetobacter calcoacetius (Herellea vaginicola)*: clinical and laboratory studies. Medicine. 56: 79-97.

Go ES, Urban C, Burns J, *et al*., (1994). Clinical and molecular epidemiology of Acinetobacter infections sensitive only to polymyxin B and sulbactum. Lancet. 344: 1329-1332.

Gordon NC, Wareham DW (2009). A review of clinical and microbiological outcomes following treatment of infections involving multidrug -resistant *A. baumannii* with tigecycline. J Antimicrob Chemother. 63: 775-780.

Gould IM (2008). The epidemiology of antibiotic resistant. Int J Antimicrob Agents. 32(suppl. 1):S2-9.

Halstead DC, Abid J, Dowzicky MJ (2007). Antimicrobial susceptibility among *Acinetobacter calcoaceticus baumannii* complex and enterobacteriaceae collected as part for the Tigecycline Evaluation and Surveillance Trail. J Infect. 55: 49-57.

Hanlon GW (2005). The emergence of multidrug resistance *Acinetobacter* species: a major concern in hospital setting. Lett Appl Microbial. 41: 375-378.

Haseley SR, Pantophlet R, Brade L, Holst O and Brade H (1997). Structural and serological characterization of the O-antigenic polysaccharide of the liposaccharide from Acinetobacter juni strain 65. Eur J Biochem. 245: 477-481.

Hawley JS, Murray CK, Jorgensen JH (2008). Colistin heteroresistance in Acinetobacter and its association with previous colistin therapy. Antimicrob Agents Chemother. 52: 351-352.

Helfand MS and Bonomo RA (2003). β-lactamase: a survey of protein diversity. Curr Drug Targets Infect Disord. 3: 9-23.

Henriksen SD (1973). *Moraxella, Acinetobacter* and the *Mimeae*. Bacteriol Rev. 37: 522-561.

Heritier C, Poirel L and Nordmann P (2006). Cephalosporinase over -expression resulting from insertion of ISAbal in *A. baumannii*. Clin Microbiol Infect. 12: 123-130.

Heritier C, Poirel L, Fournier PE, Claverie JM, Raoult D, Nordmann P (2005). Characterization of the naturally occurring oxacillinase of *Acinetobacter baumannnii*. Antimicrob Agents Chemother. 49: 4174-4179.

Heritier C, Poirel L, Lambert T, Nordmann P (2005). Contribution of acquired carbapenem-hydrolyzing oxacillinase to carbapenem resistant *A. baumannii*. Antimicrob Agents Chemother. 49: 3198-3202.

Herzberg C, Friedrich A and Averhoff B (2000). ComB, a novel competence gene required for natural transformation of *Acinetobacter sp*. BD413: identification, characterization, and analysis growth-phase -dependent regulation. Arch. Microbiol. 173: 220-228.

Higgins PG, Wisplinghoff H, Stefanik D, Seifert H (2004). In vitro activities of the β-lactamase inhibitors clavulanic acid ,sulbactum, and tazobactum alone or in combination with β-lactams gaainsts epidemiologically character multidrug -resistant *A. baumannii* strains. Antimicrob Agents Chemother. 48: 1586-1592.

http://en.wikipedia.org/wiki/nosocomial infection. Retrived on 9th Feburary 2012

http://microbewiki.kenyon.edu/index.php/Acinetobacter_baumannii.Retrived on 9th Feburary 2012.

Huang ZM, Mao PH, Chen Y, Wu L and Wu J (2004). Study on the molecular epidemiology of SHV type beta lacatamse encoding genes of multiple drug resistant *A. baumannii*. Zhonghua Lia Xing Bing Xue Za Zhi. 25: 425-427.

Hujer KM, Hamza NS, Hujer AM, Perez F, Helfand MS, Bethel CR, *et al*., (2005). Identifaction of a new allelic variant of the *Acinetobacter baumannii* cephalosporinase ,ADC 7β- lactamase : defining the unique famil of Class C enzymes. Antimicrob Agents Chemother. 49: 2941-2948.

Hujer KM, Hujer AM, Hulten EA, Bajaksouzian S and Adams JM, *et al*., (2006). Analysis of antibiotics resistance genes in multidrug-resistance *Acinetobacter* isolates from military and civilian patients treated at the Walter Army Medical Center. Anitmicrob Agents Chemother. 50: 4114-4123.

Huys G, *et al*., (2007).Biodiversity of chloramphenicol-resistant mesophilic heterotrophs from Southeast Asian aquaculture environments. Res Microbiol. 158: 228-235.

Ioannis K, Neonakis D, Spandidos A, Petinaki, E (2010). Confronting multidrug-resisatant *A. baumannii*: review. Int J Antimicrobiol Agents. (XXX-XXX).

Jason JS, Debra AG, Kurt BS and Julie E (2007). Mangino. Early Experience with Tigecycline for Ventilator-Associated Pneumonia and Bacteremia Caused by Multidrug-Resistant *A. baumannii*. Pharmacotherapy. 27: 980-987.

Jawad A, Seifert H, Snelling AM, Heritage J and Hawkey PM (1998). Survival of *A. baumannii* on dry surfaces: comparision of outbreak and sporadic isolates. J Clin Microbiol. 36: 1938-1941.

Joly-Guillou ML (2005). Clinical impact and Pathogeincity of *Acinetobacter*. Clin Microbial Infect. 11: 868-873.

Kallel H, Hergafi L, Bahloul M, Hakim A, Dammak H, Chelly H, *et al*., (2007). Safety and efficacy of colistin compared with imipenem in the treatment of ventilator -associated pneumonia: a matched case -control study. Intensive Care Med. 33: 1162-1167.

Karageorgopoulos DE, Falagas ME (2008). Current control and treatment of multidrug -resistant *A. baumannii* infections. Lancet. 8: 751-761.

Kasiakou SK, Michalopolous A, Soteriades ES, Samonis G, Sermaides GJ and Falagas ME (2005). Combination therapy with intravenous colistin for management of infections sues to multidrug resistance gram negative in patients without cystic fibrosis. Antimicrob Agents Chemother. 49: 3136-3146.

Kim SA, Yoo SM, Hyun SH, Choi CH, Yang SY, Kim HJ, *et al*., (2008). Global gene expression patterns and induction of innate immune response in human laryngeal epithelial cells in response to *A. baumannii* outer membrane protein A. FEMS Immunol Med Microbiol. 54: 45-52.

Knox L, Cooray A and Eisenstein D (2001). Probing Early Structure Formation with Far-Infrared Background Correlations. The Astrophysical Journal. 550: 7-20.

Ko KS, Suh JY, Kwon KT, *et al*., (2007). High rates of resistance to colistin and polymyxin B in subgroups of *A. baumannii* isolates from Korea. J Antimicrob Chemother. 60: 1163-1167.

Ko WC, Lee HC, Chang SR, Yan JJ, Stefanik D, Seifert H (2004). Invitro and invivo activity of meropenem and sulbactum against a multidrug -resistant *A. baumannii* strains. J Antimicrob Chemother. 53: 393-395.

Koneman WE, Allen DS, Janda M, Schreckenberger CP, Winn CW (1997). Acinetobacter. In color atlas and Textbook of Diagnostic Microbiology.7th edition, JB Lipincott Company, Philadelphia,

Kwa AL, Loh C, Low JG, Kurup A, Tam VH (2005). Nebulized colistin in tne treatment of pneumonia due to multidrug -resistant *A. baumannii* and *Pseudomonas aeruginosa*. Clin Infect Dis. 41: 754-757.

Lee HW, Kah YM, Kim J, Lee JC, Seol SY, Cho DT, *et al*., (2008). Capacity of multidrug resistant clinical isolates of *A. baumannii* to form biofilm and adhere to epithelial cell surfaces. Clin Microbiol Infect. 14: 49-54.

Lee JH, et *al*., (2007). Differences in phenotypic and genotypic traits against antimicrobial agents between *Acinetobacter baumanii* and *Acinetobacter* genomic species 13TU. J Antimicrob Chemother. 59: 633-639.

Lee K, Ha GY, Shin BM, Kim JJ, Kang JO, Jang SJ, Yong D and Chong Y (2004). Metallo-beta-lacatamase producing Gram negative bacilli in Korean Nationalwide Survelliance of Antimicrobial Resistance Group hospitals in 2003: continued prevalence of VIM-producing *Pseudomonas spp*. and increase of IMP-producing *Acinetobacter spp.* Diagn Microbiol Infect Dis. 50: 51-58.

Lee NY, Wang CL, Chuang YC, Yu WL, Lee HC, Chang CM, *et al*., (2007). Combination carbapenem -sulbactum therapy for critically ill patients with multidrug-resistant *A. baumannii* bactermia: four case reports and an in vitro combination synergy study. Pharmacotherapy. 27: 1506-1511.

Li J, Rayner CR, Nation RL, Owen RJ, Spelman D, Tan KE, *et al*., (2006). Heteroresistance to colistin in multidrug-resistant *A. baumannii*. Antimicrob Agents Chemother. 50: 2946-2950.

Linden PK, Paterson DL (2006). Parenteral and inhaled colistin for the treatment of ventilator-associated pneumonia.Clin Infect Dis. (suppl.2):S89-94.

Livermore DM (1995). β-lactamase in laboratory and clinical resistance. Clin Microbiol Rev. 8: 557-584,

Livermore DM (2005). Tigecycline: what is it and where should it be used: J Antimicrob Chemother, 56: 611-614.

Lolans K, Rice TW, Munoz-Price LS and Quinn JP (2006). Multicity outbreak of carbapenem resistant *A. baumannii* isolates producing the carbapenemase OXA-40. Antimicrob Agents Chemother. 50: 2941-2945.

Magnet S, Courvalin P and Lambert T (2000). Resistance -nodulation -celldivision -type efflux pump involved in aminoglycoside resistance in *A. baumannii* strain BM4454. Antimicrob Agents Chemother. 45: 3375-3380.

Majiduddin FK, Materon IC and Palzkii TG (2002). Molecular analysis of β-lactamase structure and function. Int J Med Microbiol. 29: 127-137.

Maragakis LL, Cosgrove SE, Song X, *et al*., (2004). An outbreak of multidrug-resistant *A. baumannii* associated with pulsative lavage wound treatment. JAMA. 292: 3006-3011.

Maragakis LL, Perl TM (2008). *A. baumannii*: epidemiology, antimicrobial resistant, and treatment options. Clin Infect Dis. 46: 1254-1263.

Marchaim D, Navon-Venezia S, Leavitt A, Chemelnitsky I, Schwaber MJ, Carmeli Y (2007). Molecular and epidemiologic study of polyclonal outbreak of multidrug resistant *A. baumannii* infection in an Israeli hospital. Infect Control Hosp Epidemiol. 28: 945-950.

Marchand I, Damier-Piolle L, Courvalin P and Lambert T (2004). Expression of the RND-type efflux pump AdeABC in *A. baumannii* is regulated by the AdeRS two -component system. Antimicrob Agents Chemother. 48: 3298-3304.

Maslow JN, Glaze T, Adams P, Lataillade M (2005). Concurrent outbreak of multidrug -resistant and susceptible subclones of *A. baumannii* affecting different wards of asingle hospitals. Infect Control Hosp Epidemiol. 26: 69-75.

Maviglia R, Nestorini R, Pennisi M (2010). Role of old antibiotics in multidrug resistance bacteria infections. Curr Drug targets. 10: 895-905.

Metzgar D, Bacher JM, Pezo V, Reader J, Doring V, Schimmel P, Marliere P and de Crecy- Lagard V (2004). *Acinetobacter spp.* ADP1: an ideal model organism for genetic and genome engineering. Nucleic Acids Res. 32: 5780-5790.

Michalopoulos A, Fotakis D, Virtzil S, *et al*., (2008). Aerosolized colistin as adjunctive treatment of ventilator - associated pneumonia due to multidrug resistant Gram negative bacteria: a prospective study. Respir Med. 102: 407-412.

Moore IF, Hughes DW, Wright GD (2005). Tigecycline is modification by the flavin-dependent monooxygenase TetX. Biochemistry. 44: 11829-1135.

Morgan DJ, Weisenberg SA, Augenbraun MH, Calfee DP, Currie BP, Furuya EY, *et al*., (2009). Multidrug-resistance *A. baumannii* in new York City-10 years into the epidemic. Infect Control Hosp Epidemiol. 30: 196-207.

Moubareck C, Bremont S, Conroy MC, Courvalin P, Lambert T (2009). GES-11, a novel integron- associated GES variant in *A. baumannii*. Antimicrob Agents Chemother. 53: 3579-3581.

Mussi MA, Limansky AS, Viale AM (2005). Acquisitation of resistance to carbapenems in Multidrug-resistance clinical strains of *A. baumannii*: natural insertional inactivation of a gene encoding a member of a novel family of β-barrel outer membrane proteins. Antimicrob Agents Chemther. 49: 1432-1440.

Naas T, Bogaerts P, Bauraing C, Deghldre Y, Glupezynski Y and Nordmann P (2006). Emergence of PER and VEB extended spectrum beta-lacatamses in *A. baumannii* in Belgium. J Anitmicrob Chemother. 58: 178-182.

Naas T, Coignard N, Carbonne A, Blanckaert K, Bajolet O, Bernet C, Verdeil X, Astagneau P, Desenclos JC and Nordmann P (2006). VEB-1 Extended-spectrum beta lactamase producing *A. baumannii* in France. Emerg Infect Dis. 12: 1214-1222.

Nagano N, Nagano Y, Cordevant C, Shibata N and Arakawa Y (2004). Nosocomial transmission on the CTX-M- 2 β-lactamase producing *A. baumannii* in a neurosurgery ward. J Clin Microbiol. 43: 3978-3984.

Navon-Venezia S, Leavitt A and Carmeli Y (2007). High tigecycline resistant in multidrug-resistant *A. baumannii*. J Antimicrob Chemother. 59: 772-774.

Oncul O, *et al*., (2002). Hospital acquired infection following the 1999 Marmara earthquake. Hosp Infect. 51: 47-51.

Pantopoulou A, *et al*., (2007). Colistin offers prolonged survival in experimental infections by multidrug -resistant *A. baumannii*: the significance of co-administration of rifampicin. Int J Antimicrob Agents. 29: 51-55.

Paterson DL (2006). The epidemiology profile of infections with multidrug resistance *Pseudomonas aeuroginosa* and *Acinetobacter* species. Clin Infect. Dis. 43(supp.2): S43-48.

Paul G H, Wisplinghoff H, Stefanik D and Seifert H (2004). In Vitro Activities of the β-Lactamase Inhibitors Clavulanic Acid, Sulbactam, and Tazobactam alone or in Combination with β-Lactams against Epidemiologically Characterized Multidrug-Resistant *A. baumannii* Strains. Antimicrob Agents Chemother. 48 (5): 1586–1592.

Peleg AY, Adams J, Paterson DL (2007). Tigecycline effilux as a mechanism for non susceptibility in *A. baumannii*. Antimicrob Agents Chemother. 51: 2065-2069.

Peleg AY, Potoski BA, Rea R, Adams J, Sethi J, Capitano B, Husain S, Kwak EJ, Bhat SV and Paterson DL (2007). *A. baumannii* bloodstream infection while receiving tigecycline:a cautionary report. J Antimicrob Chemother. 59: 128-131.

Peleg AY, Seifert H, Paterson DL (2008). *A. baumannii*: emeregence of successful pathogens. Clin Microbiol Rev. 21: 538-582.

Perez F, Hujer KM, Decker BK, Rather PN, Bonomo RA (2007).Global challenge of Multidrug resistance *A. baumannii.* Antimicrob Agents Chemother. 51: 3471-3484.

Poirel L, Cabanne L, Vahaboglu H and Nordmaan P (2005). Genetic environment and expression of the β-lactamase *bla* $_{PER-1}$ gene in gram negative bacteria. Antimicrob Agents Chemother. 49: 1708-1713.

Poirel L, Corvec S, Rapoport M, Mugnier P, Petroni A, Pasteran F, *et al*., (2007). Identifaction of novel narrow spectrum β-lactamase SCO-1 in *Acinetobacter spp*. from Argentia. Antimicrob Agents Chemother. 51: 2179-2184.

Poirel L, Menutau O, Agoli N, Cattoen C and Nordmann P (2003). Outbreak of extended spectrum β-lactamse VEB-1 producing isolates of *Acinetobacter* in French hospitals. J Clin Microbiol. 41: 3542-3547.

Poirel L, Nordmann P (2006). Carbapenem resistance in *A. baumannii*: mechanisms and epidemiology. Clin Microbiol Infect. 12: 826-836.

Poole K (2004). Efflux mediated multiresistance in Gram negative bacteria. Clin Microbiol Infect. 18: 12-26.

Principle L, Arezzo DS, Capone A, Petrosillo N, Visca P (2009). Invitro activity of tigecycline in combination with various antimicrobials against multidrug resistant *A. baumannii*. Ann Clin Microbiol Antimicrob. 8: 18.

Rafailidis PI, Ioannidou EN, Falagas ME (2007). Ampicllin /sulbactam: current status in severe bacterial infections. Drugs. 67: 1829-1849.

Ray YH, *et al*. (2007). Colistin Is Effective in Treatment of Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa* in Cancer Patients. Antimicrob Agents Chemother. 51(6): 1905–1911.

Reiner RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ (2007). Antimicrobial susceptibility among organisms from Asia Pacific Rim, Europe and Latin and North America collected as a part of TEST and the in vitro activity of tigecycline. J Antimicrob Chemother. 60: 1018-1029.

Reis AO, Luz DA, Tognim MC, Sader HS and Gales AC (2003). Polymyxin- resistant *Acinetobacter spp*. isolates: what is next? Emerg Infect Dis. 9: 1025-1027.

Robicsek A, Sahm DF, Strahilevitz J, Jocoby GA, Hoeper DC (2005). Broader distribution of plasmid -mediated quinolone resistant in the United States. Antimicrob Agents Chemother. 49: 3001-3003.

Rodriguez Guardado A, Blanco A, Asensi V, *et al*., (2008). Multidrug -resistant acinetobacter meningitis in neurosurgical patients with intraventicular catheters: assessment of different treatments. Antimicrob Chemother. 61: 908-913.

Rowe-Magnus DA and Mazel D (2002). The role of integrons in antibiotic resistance gene capture. Int J Med Microbiol. 292: 115-125.

Ruzin A, Keeney D, Barford PA (2007). AdeABC multidrug efflux pump is associated with decreased susceptibility to tigecycline in *Acinetobacter calcoaceticus-A. baumannii complex*.J Antimicrob Chemother. 59: 1001-1004.

Sader HS, Rhomberg PR, Jones RN (2005). In vitro activity of beta-lactam antimicrobial agents in combination with aztreonam tested against metallo-beta lactamase -producing *Pseudomonas aeroginosa* and *A. baumannii.* J Chemother. 17: 622-627.

Saeed S, Fakih MG, Riederer K, Shah AR, Khabit R (2006). Interinstitutional and intrainstitutional transmission of a strain of *A. baumannii* detected by molecular analysis: comparison of pulse gel electrophoresis and repetitive sequence based polymerase chain reaction. Infect Control Hosp Epidemiol. 27: 981-983.

Scheetz MH, Qi C, Warren JR, *et al*., (2007). In vitro activities of various antimicrobials alone and in combination with tigecycline against carbapenem -intermediate or resistant *A. baumannii*. Antimicrob Agents Chemother. 51: 1621-1626.

Scott P, *et al*., (2007). An outbreak of multidrug -resistant *A. baumannii-calcoacetius complex* infection in the US military health care system associated with military operations in Iraq. Clin Infect Dis. 44: 1577-1584.

Seifert H and Gerner-Smitdt P (1995). Comparison of ribotyping and pulsed-field gel electrophoresis for molecular typing of *Acinetobacter* isolates. J Clin Microbiol, 33: 1402-1407.

Seifert H, *et al*., (1997). Distribution of *Acinetobacter* species on Human skin: comparision of phenotypic and genotypic identification methods. J Clin Microbiol. 35: 2819-2825.

Siu LK (2002). Antibiotics: action and resistance in gram -negative bacteria. J Microbiol Immunol Infect. 35: 1-11.

Smith MG, Gianoulis TA, Pukatzki S, Mekalanos JJ, Ornston LN, Gerstein M, *et al*., (2007). New insights into *A. baumannii* pathogenesis revealed by High density pyrosequencing and transposon mutagenesis. Genes Dev. 21: 601-614.

Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, *et al*., (2003). Nosocomial multi-drug resistant *A. baumannii* blood stream infection: risk factors and outcome with ampicllin -sulbactum treatment. J Hosp Infect. 54: 32-38.

Somor AE, Lee M, Vearnocombe M, *et al*., (2002). Clinical and molecular epidemiology of *A. baumannii* in a burn unit: risk factors for acquiatation and management .Infect Control Hosp Epidemiol. 23: 261-267.

Song JY, Kee SY, Hwang IS, *et al*., (2007). In vitro activities of carbapenem /sulbactum combination, colistin colistin/rifampicin combination and tigecycline against carbapenem -resistant *A. baumannii.* J Antimicrob Chemother. 60: 317-322.

Srinivasan VB, Rajamohan G, Gebreyes WA (2009). The role of a novel efflux pump AbeS, member of the SMR family of transporters in resistant to antimicrobial agents in Acinetobacter bauamnnii. Antimicrob Agents and Chemother. 53: 5312-5316.

Su XZ, Chen J, Mizushima T, Kuroda T and Tsuchiya T (2005). AbeM an H+ coupled *A. baumannii* multidrug efflux pump belonging to the MATE family of transporter .Antimicrob Agents Chemother. 49: 4362-4364.

Taccone FS, Roderguez-Villalobos H, De Backer D, De Moor V, Deviere J, Vincent JL and Jacobs F (2005). Successful treatment of septic shock due to pan-resistant *A. baumannii* using combined antimicrobioal therapy including tigecycline. Eur J Clin Microbiol Infect Dis. 25: 257-260.

Tjernberg I and Ursing J (1989). Clinical strains Acinetobacter classified by DNA-DNA hybridization. APMIS. 97: 595-605.

Tognim MC, Gales AC, Penteado AP, Sibert S, Sader HS (2006). Dissemination of IMP-1 metallo beta lactamase producing *Acinetobacter species* in a Brazilian teaching hospital . Infect Control Hosp Epidemiol. 27: 742-747.

Tripodi MF, Durante-Mangoni E, Fortunato R, Utilli R, Zarrilli R (2007). Comparative activities of colistin , rifampicin, imipenem and sulbactum/ampicillin alone or in combination against epidemic multidrug-resistant *A. baumannii* isolates producing OXA-58 carbapenemase. Int J Antimicrob Agents. 30: 537-540.

Turton JF, Ward ME, Woodford N, Kaufmann ME, Pike R, Livermore DM, *et al*., (2006).The role of ISAba1 in expression of OXA carbapenemase genes in *A. baumannii*. FEMS Microbiol Lett. 258: 72-77.

Vallenet D, Nordmann P, Barbe V, Poirel L, Mangenot S, Bataille E, *et al.*, (2008). Comparative analyisi of *Acinetobacters*:three genomes for three lifestyles.PLoS One. 19: e1: 805.

Van den Broek, PJ, Arends J, Bernards AT, *et al*., (2006). Epidemiology of multiple *Acinetobacter* outbreaks in the Neatherlands during the period 1999-2001. Clin Microbiol Infect. 12: 837-843.

Van Dessel H, Dijkshroorn L, Van der Reijden T, Bakker N, Paauw A, van den Broek P, Verhoef J and Brisse (2004). Identification of a new geograpohically widespread multidrug resistant *A. baumannii* clone from European hospitals. Res Microbiol. 155: 105-112.

Van Looveren M, Goosens H (2004). ARPAC Steering Group. Antimicrobial resistance of *Acinetobacter spp*. In Europe. Clin Microbiol Infect. 10: 684-704.

Vidal R, Domingeuz M, Urrutia H, Bello H, Gonzales G, Garcia A, *et al*., (1996). Biofilm formation by *A. baumannii*. Microbios. 86: 49-58.

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Vila J, Marti S, Sanchez -cespedes J (2007). Porins, efflux pumps and multidrug resistance in *A. baumannii*. J Antimicrob Chemother. 59: 1210-1256.

Vila J, Pachon J (2008). Therapeutic option for *A. baumannii* infections. Expert Opin Pharmacother. 9: 587-599.

Vila J, Ruiz J, Goni P, Jimenez de Anta T (1997). Quinolones -resistant mutations in the topoisomerase IV *parC* gene of *A. baumannii*. J Antimicrob Chemother. 39: 757-762.

Vila J, Ruiz J, Goni P, Marcos A, Jimenez de Anta T (1995). Mutation in the *gyrA* gene of quinolone -resistant clinical isolates of *A. baumannii*. Antimicrob Agents Chemother. 39: 1201-1213.

Von Graevenitz A(1995). *Acinetobacter bauamnnii, Alcaligenes, Moraxella,* and other non fermenatative Gram-negative bacteria.In: Murry PR,Barons JE,Pfaller MA,Tenover FC,Yolken RH, editors.manual of clinical microbiology.Washington, DC: ASM Press.p520-32.

Walsh TR (2005). The emergence and implications of metallo beta-lactamase in Gram negative bacteria. Clin Microbiol Infect. 11(suppl-6)2-9.

Walsh TR, Toleman MA, Poirel L and Nordmann P (2005). Metallo beta lactamase: the quite before the strom? Clin Microbiol Rev. 18: 306-325.

Wisplinghoff H, Schmitt R, Wohramnn A, Stefanik D and Seifert H, Resistance to disinfectants in epidemiologically defined clinical isolates of *A. baumannii*. J Hosp Infect. 66: 174-181. (2007).

Wolf M, Joly -Guillou MR, Farinotti R, Carbon C (1999). In vivo efficacies of combinations of β-lactams, β-lactamase inhibitors and rifampin against *A. baumannii* in a mouse pneumonia model. Antimicrob Agents Chemother. 43: 1406-1411.

Wyant SR, Moss WC, Weaver ER, Hollis GD, Jordan GJ, Cook CE (1996). Daneshvar IM, Identification of unusual pathogenic Gram negative aerobic and faculatative anaerobic bacteria.Second edition ,Williams andWilkins.

Yau W, Owen RJ, Poudyal A, Bell JM, Turnidge JD, Yu HH, *et al*., (2009).Colistin heteroresistance in multidrug-resistant *A. baumannii* clinical isolates from the Western Pacific region in the SENTRY antimicrobial surveillance programme. J Infect. 58: 138-144.

Young DM and Ornston LN (2001). Functions of the mismatch repair gene *mutS* from *Acinetobacter sp.* strain ADP1. J Bacteriol. 183: 6822-6831.

Yum JH, Yi K, Lee H, Yong T, Lee K, Kim JM, *et al*., (2002). Molecular characterization of metallo beta lactamase producing *A. baumannii* and Acinetobacter genomospecies 3 from Korea: identification of two new integrons carrying the bla_{VIM-2} gene cassettes. J Antimicrob Chemother. 49: 837-840.

Zavascki AP, Carvalhaes CG, Picao RC, Gales AC (2010). Multidrug resistance *Pseudomonas aeuroginosa* and *A. baumannii*: resistance mechanisms and implications for therapy. Expert Rev Anti Infect Ther. 8: 71-93.

Zimbler DL, Penwell WF, Gaddy JA, Menke SM, Tomaras AP, Connerly PL, *et al*., (2009). Iron acquisition functions expressed by the human pathogen *A. baumannii*. Biometals. 22: 23-32.