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REVIEW

Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside

Ming-Feng Lin, Chung-Yu Lan

Ming-Feng Lin, Chung-Yu Lan, Institute of Molecular and Cellular Biology, National Tsing Hua University, Hsin-Chu 31064, Taiwan
Ming-Feng Lin, Department of Medicine, National Taiwan University Hospital Chu-Tung Branch, Hsin-Chu 31064, Taiwan
Author contributions: Lin MF and Lan CY contributed to this paper; both authors read and approved the final version of the manuscript before submission.
Correspondence to: Ming-Feng Lin, MD, Chief of Department of Medicine, National Taiwan University Hospital Chu-Tung Branch, No. 52, Chih Shan Road, Chutung Town, Hsin-Chu 31064, Taiwan. c9977@ms27.hinet.net
Telephone: +886-35-943248 Fax: +886-35-308630
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Abstract

Acinetobacter baumannii (*A. baumannii*) is undoubtedly one of the most successful pathogens in the modern healthcare system. With invasive procedures, antibiotic use and immunocompromised hosts increasing in recent years, *A. baumannii* has become endemic in hospitals due to its versatile genetic machinery, which allows it to quickly evolve resistance factors, and to its remarkable ability to tolerate harsh environments. Infections and outbreaks caused by multidrug-resistant *A. baumannii* (MDRAB) are prevalent and have been reported worldwide over the past twenty or more years. To address this problem effectively, knowledge of species identification, typing methods, clinical manifestations, risk factors, and virulence factors is essential. The global epidemiology of MDRAB is monitored by persistent surveillance programs. Because few effective antibiotics are available, clinicians often face serious challenges when treating patients with MDRAB. Therefore, a deep understanding of the resistance mechanisms used by MDRAB can shed light on two possible strategies to combat the dissemination of antimicrobial resistance: stringent infection control and antibiotic treatments, of which colistin-based combination therapy is the mainstream strategy. However, due to the current unsatisfying therapeutic outcomes, there is a great need to develop and evaluate the efficacy of new antibiotics and to understand the role of other potential alternatives, such as antimicrobial peptides, in the treatment of MDRAB infections.

Key words: *Acinetobacter baumannii*; Antibiotic resistance; Epidemiology; Genomics; Infection control

Core tip: With the current rapid increase in the numbers of studies on Acinetobacter baumannii (*A. baumannii*), the complexity of the entire picture regarding how this superbug copes with its environment and influences human beings is gradually being understood. By conducting a thorough review of this topic, this paper aims to present the relevant literature regarding the antimicrobial resistance of *A. baumannii* and the currently available treatment options for *A. baumannii* infections to highlight possible future research directions.

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INTRODUCTION

Species identification and current taxonomy

Acinetobacter spp. are glucose-non-fermentative, non-motile, non-fastidious, catalase-positive, oxidase-negative, aerobic Gram-negative coccobacilli[1]. Since 1986, the taxonomy of the genus *Acinetobacter* has been modified several times. Currently, the original single species clas-

sification of *Acinetobacter calcoaceticus (A. calcoaceticus)* has been abandoned, and at least 34 genomic species can be distinguished within the genus *Acinetobacter*, 23 of which have been assigned species names[2]. The challenge in the taxonomy of *Acinetobacter* is due to the clusters of closely related species that are difficult to distinguish using phenotypic traits and chemotaxonomic methods. The *A. calcoaceticus-Acinetobacter baumannii (A. baumannii)* complex, comprising *A. calcoaceticus*, *A. baumannii*, and the genomic species 3 and 13TU, is the most well-known example[3]. Because the antibiotic susceptibilities and clinical relevance of the different genomic species are significantly different[4-7], genomic methods for *Acinetobacter* species identification are necessary. A number of genomic fingerprinting methods have been proposed, including pulsed-field gel electrophoresis (PFGE); ribotyping; polymerase chain reaction (PCR)-based fingerprinting techniques, such as random amplified polymorphic DNA analysis; repetitive extragenic palindromic sequence-based PCR (rep-PCR); amplified ribosomal DNA restriction analysis; RNA spacer fingerprinting; and amplified fragment length polymorphism analysis[8]. In addition, new methods, such as 16S-23S ribosomal intergenic spacer, 16S rRNA gene, *rpoB* gene and *gyrB* gene sequence analyses, have been developed for *Acinetobacter* species identification[9,10].

Common typing methods in outbreak investigations

Of all of the *Acinetobacter* species, *A. baumannii* is the most important member associated with infections in clinical practice and causes most of the reported outbreaks. In addition to chart review and statistical epidemiology, some DNA fingerprinting methods are valuable in outbreak investigations and strain discrimination. Rep-PCR, PFGE, and multilocus sequence typing (MLST) have all been used in previous studies. Rep-PCR has been proven to be a useful and expedient method for the epidemiological characterization of *A. baumannii* nosocomial outbreaks[11]. Rep-PCR has also been used as a tool for determining species lineages of *A. baumannii* in a hospital[12] and for differentiating pan-European, multi-resistant *A. baumannii* clone Ⅲ from clones Ⅰ and Ⅱ[13]. Despite the inter-laboratory variability of rep-PCR, this method has the advantage of being faster to perform than PFGE and MLST. The intra-laboratory clustering of *A. baumannii* has been shown to be well conserved[14] and to correlate well with PFGE[15] or MLST results[16], demonstrating the robustness of rep-PCR. We have found one rep-PCR major cluster (84%) of *A. baumannii* carrying a class I integron that spread among four regional hospitals in northern Taiwan[17]. However, PFGE is still considered the gold standard for typing outbreak-related isolates of *A. baumannii*[18-21], whereas MLST provides a high level of resolution and is an excellent tool for studying the population structure and long-term epidemiology of *A. baumannii*[22]. Recently, the *A. baumannii* MLST database (http://pubmlst.org/abaumannii/) was developed for the BIGSdb genomics platform[23] to assist the broader community in elucidating the structure and function of this microorganism.

Clinical manifestations

A. baumannii, named after Paul Baumann, is ubiquitous in soil and water[24]. Previously, *A. baumannii* was regarded as a low-virulence commensal bacterium. However, it has become a successful pathogen[25] and has emerged as a major cause of healthcare-associated infections, most of which have occurred in critically ill patients in the intensive care unit (ICU) setting[26]. In recent decades, infections caused by *A. baumannii* have also occurred outside the ICU or in trauma patients after natural disasters, and they have even affected patients with co-morbidities in the community[27]. Reports of community-acquired *Acinetobacter* infections have increased over the past decade[28]. Several different types of infections, including pneumonia, urinary tract infections, bacteremia, wound infections and even meningitis, are caused by this organism[29]. These infections often occur in older patients, many of whom have chronic underlying diseases and have previously received antimicrobial treatment[30,31]. The mortality of patients with *A. baumannii* infections in hospitals and in the ICU has ranged from 7.8% to 23% and from 10% to 43%, respectively[32].

Risk factors

In recent years, many studies have reported the risk factors for acquiring *A. baumannii* infections and have particularly focused on those caused by multidrug-resistant strains. The acquisition of MDRAB is related to multiple factors, including environmental contamination and contact with transiently colonized healthcare providers[33]. The independent risk factors for the acquisition of imipenem-resistant *A. baumannii* (IRAB) include a hospital size of > 500 beds, previous antimicrobial treatment, a urinary catheter, surgery[34], previous ICU stay, and prior exposure to imipenem or third-generation cephalosporins[35]. The only significant independent risk factor for the appearance of imipenem-resistant multidrug-resistant *A. baumannii* (MDRAB) in patients formerly infected with imipenem-susceptible MDRAB is imipenem or meropenem exposure[36]. For extensively drug-resistant *A. baumannii* (XDRAB) infections, the prior use of imipenem, meropenem, piperacillin/tazobactam or fourth-generation cephalosporins and > 30 d of being bedridden have been found to be independent risk factors[37]. A systematic review concluded that the acquisition and spread of *A. baumannii* appeared to be related to a large number of variables, the most important of which were deficiencies in the implementation of infection control guidelines and the use of broad-spectrum antibiotics[38].

The risk factors that are associated with *A. baumannii* bacteremia are immunosuppression, unscheduled hospital admission, respiratory failure at ICU admission, previous antimicrobial therapy, previous sepsis in the ICU, and the invasive procedures index[39]. Resistance to carbapenems, mechanical ventilation, and the presence of malignancy have also been found to be associated with high mortality rates in patients with *A. baumannii* bacteremia[40].

Regarding ventilator-associated pneumonia caused by *A. baumannii*, the risk factors include neurosurgery, adult respiratory distress syndrome, head trauma, and large-volume pulmonary aspiration[41]. Because various studies showed certain differences in the risk factors of acquiring drug-resistant *A. baumannii* bacteremia or pneumonia[42-46], a separate investigation should be performed in each hospital setting to limit the spread of this pathogen[38].

Virulence factors

Previously, *A. baumannii* was regarded as a low-grade pathogen; however, it contains virulence factors that enhance its bacterial toxicity and pathogenicity. A combined approach of genomic and phenotypic analyses led to the identification of several virulence factors, including extracellular components with hemolytic, phospholipase, protease and iron-chelating activities, biofilm formation, surface motility, and stress resistance[47]. The biofilm formation of *A. baumannii* facilitates its attachment to abiotic and biotic surfaces[48], including those of medical devices and host tissues. The initiation and maturation of biofilms are related to pilus assembly and the production of the biofilm-associated protein (Bap), which is regulated by the two-component system BfmRS[49]. The Bap protein plays a role in adhesion to human epithelial cells[50], and the inhibition of this protein can prevent *A. baumannii* infection[51]. In fact, in a multicenter cohort study, all catheter-related urinary or blood stream infections due to *A. baumannii* were caused by biofilm-forming strains[52]. A 2D proteomic analysis of pellicle-forming *A. baumannii* isolates showed that overexpression of CarO, which is an OprD-homolog, siderophore iron uptake, and pili systems are involved in the development of biofilms[53].

Iron uptake systems are essential to the survival and pathogenicity of bacteria, especially in the low-iron environment of the human host. *A. baumannii* grown under iron-limited conditions undergo major transcriptional changes of not only many iron acquisition-related genes but also of genes involved in motility[54]. *A. baumannii* is well-equipped with metal homeostatic systems that are required for the colonization of a diverse array of tissues[55]. Genome investigations have revealed wide distributions of endogenous siderophores in clinical *A. baumannii* isolates, arguing for their role in pathogenic capabilities[47]. The zinc acquisition system has also been found in *A. baumannii,* which is required for efficient zinc uptake *in vitro* and full pathogenesis *in vivo*[56].

A. baumannii adheres to human bronchial epithelial cells *in vitro*, and its prevalent European clone Ⅱ has a relatively high capacity for adhering to these cells[57]. Additionally, the K1 capsular polysaccharide has been shown to prevent *A. baumannii* from being phagocytized by macrophages, to optimize its growth in human ascites fluid and serum, and to enhance its survival in a rat soft tissue infection model[58]. Moreover, several proteins have been implicated as possible virulence factors in *A. baumannii*. Omp38 induces the apoptosis of host cells[59], the absence of the RecA protein decreases survival in response to both heat shock and desiccation[60], and the inactivation of phospholipase D diminishes *A. baumannii* pathogenesis[61]. Importantly, the outer membrane protein A of *A. baumannii* (AbOmpA) is the most abundant surface protein that has been associated with the apoptosis of epithelial cells through mitochondrial targeting[62]. AbOmpA is also the major nonspecific channel in *A. baumannii* and appears to be essential for this organism's high levels of intrinsic resistance to a number of antibiotics[63]. *A. baumannii* can rapidly develop resistance to polymyxin antibiotics through the loss of the lipid A component of lipopolysaccharide[64], which subsequently alters the expression of critical transport and biosynthesis systems associated with modulating the composition and structure of the bacterial surface[65].

GLOBAL EPIDEMIOLOGY

Two key factors contributing to the significant and ubiquitous dissemination of *A. baumannii* in hospitals are the extent of its antimicrobial resistance and its environmental resilience[66]. The extent of antimicrobial resistance is more severe in *A. baumannii* isolates from patients in Asian and European ICUs than from patients in American ICUs[27], and significant increases in antimicrobial resistance were noted worldwide from 2004 to 2009. The highest resistance rates in 2009 were for ceftriaxone (83.6%), piperacillin-tazobactam (82.0%), and ceftazidime (80.3%) in the Middle East. Increases in resistance were noted for all antimicrobials in isolates collected from the Asia-Pacific Rim, ranging from a 19.1% increase in ceftazidime resistance to a 38.9% increase in levofloxacin resistance. Resistance also increased significantly in Africa (including piperacillin-tazobactam, ceftriaxone, cefepime, amikacin, meropenem, and levofloxacin resistance) and Europe (including piperacillin-tazobactam, ceftriaxone, ceftazidime, levofloxacin, amikacin, minocycline, meropenem, and cefepime resistance)[67].

The first MDRAB isolate resistant to almost all available antibiotics in Taiwan was discovered in 1998[68]. Since then, many MDRAB outbreaks have been reported in Taiwan[69-72]. A Taiwanese surveillance report of antimicrobial resistance in 2000 found that 73% of *A. baumannii* isolates collected from 21 medical centers and regional hospitals were ceftazidime-resistant[73]. Another study conducted during the same year at five major teaching hospitals in Taiwan showed that as many as 22% of *A. baumannii* isolates were not susceptible to imipenem[74]. In 2012, the Taiwan Surveillance of Antimicrobial Resistance program showed that the prevalence of the IRAB complex increased from 3.4% in 2002 to 58.7% in 2010 and that of the XDRAB complex increased from 1.3% in 2002 to 41.0% in 2010[75]. In addition, the proportion of healthcare-associated infections caused by carbapenem-resistant *A. baumannii* (CRAB) significantly increased, compared to infections by all *A. baumannii*, from 14% in 2003 to 46% in 2008 in Taiwan[76]. The local spread of MDRAB has been demonstrated in five proximal hospitals in northern Taiwan, with resistance determinants

distributed widely in clonal and non-clonal isolates[77].

In addition to its prevalence in Taiwan, MDRAB is also prevalent in hospitals in many areas of the world, including Korea[78], Belgium[79], Italy[80], Iraq[81], Israel[82], Greece[83] and America[84]. Furthermore, a one-year study demonstrated that three clones of MDRAB had spread in hospitals in Brazil[85]. In a single institution in Queensland, Australia, sequence type 92 (ST92) was the dominant sequence type and was present for 9 years[86]. Additionally, clonal dissemination among three hospitals located in two different cities has been documented in China, indicating the epidemic potential of MDRAB[87]. Both inter-institutional and intra-institutional transmission of a strain of *A. baumannii* is possible[15]. Several multidrug-resistant clones can coexist endemically in one hospital for several years[31,88], and the same clones often spread on a small scale within a short period of time[31] or can be detected during an outbreak by a close survey of epidemic sources[88]. Furthermore, such outbreaks can occur across national boundaries. For example, Wybo *et al*[89] reported a MDRAB nosocomial infection involving approximately 20 patients in a university hospital in Belgium that was the result of a transfer of two patients from Greece.

In addition to the increasing importance of MDRAB in nosocomial infections, the increasing reports of outbreaks caused by CRAB in recent years have become another frightening reality. The imipenem resistance rate of *A. baumannii* from a worldwide collection between 2005 and 2009 reached resistance rates of greater than 50%[90]. In Brooklyn, New York, citywide surveillance revealed that about 2 of every 3 isolates were resistant to carbapenem antibiotics[91]. One predominant strain type of CRAB has established predominance after being introduced in a university hospital in Chicago in 2005[21]. In addition, molecular epidemiological investigations of sequential outbreaks of *A. baumannii* in an ICU showed the emergence of carbapenem resistance in Italy from 1999 to 2002[19]. The clonal spread of imipenem-resistant *Acinetobacter* spp. accompanied by the wide dissemination of the OXA-23 carbapenemase has been noted in China[92]. The first CRAB outbreak was reported in America in 1991, followed by global CRAB dissemination[93]. Most outbreaks caused by CRAB have occurred in ICU settings[29,94] throughout many countries. An outbreak caused by pandrug-resistant *A. baumannii* (PDRAB) was also reported in a pediatric ICU in a Taiwanese hospital[95].

COMPARATIVE GENOMICS

In recent years, whole-genome sequencing and comparative genomics have been performed to elucidate the genetic basis of *A. baumannii* resistance, especially regarding the extent of variability and the acquisition and transfer of resistance determinants among different strains. The *A. baumannii* strain AYE, an endemic strain in France, exhibits an 86-kb resistance island in which 45 resistance genes are clustered[96]. Sequence similarities and phylogenetic analyses confirm that most of the resistance genes found in the *A. baumannii* AYE strain have been acquired from bacteria of the genera *Pseudomonas*, *Salmonella*, or *Escherichia*. Using pyrosequencing and transposon mutagenesis, the assembled genome of *A. baumannii* ATCC 17978 has been shown to consist of 3976746 base pairs (bp) and 3830 open reading frames (ORFs), a significant fraction (17.2%) of which are located in 28 putative alien islands[97]. A remarkable number of the islands contain genes implicated in virulence. *A. baumannii* ACICU has a single chromosome of 3904116 bp and two plasmids, pACICU1 and pACICU2, of 28279 and 64366 bp, respectively[98]. As many as 36 putative alien islands (pAs), 15 of which encode genes related to drug resistance, have been detected in the *ACICU* genome. One investigation involving MDRAB strains from hospitals of 10 European countries showed that AbaR3 is the original structure from which the AbaRs, the genomic islands containing many resistance genes, have been derived in European clone I, thus providing the strains of this lineage with a selective advantage[99]. All of these findings indicate that the genome of *A. baumannii* has acquired a large amount of foreign DNA, which has an important role in pathogenesis and antimicrobial resistance.

Currently, the whole-genome sequencing of the widely spread MDRAB strain MDR-ZJ06[100]; an MDR-TJ[101] strain in China; and two other multidrug-resistant strains (TCDC-AB0715, harboring both *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-66}}$[102], and TYTH-1[103] from Taiwan) has been completed. A comparative genomics analysis has revealed a common strain lineage between the Taiwanese strains (TYTH-1 and TCDCAB0715) and the Chinese strains (MDR-TJ and MDR-ZJ06)[104]. Phylogenetic studies and GC profiles showed that the genome of TYTH-1 was the closest to the genome of MDR-ZJ06, which implies that the dissemination of *bla*$_{\text{OXA-23}}$-carrying CRAB in Taiwan may have been mediated by the transfer of people between Taiwan and China.

Adams *et al*[105] found that the entire multidrug-resistance phenotype of *A. baumannii* can be explained by the acquisition of discrete resistance determinants distributed throughout the genome. A comparison of closely related multidrug-resistant and drug-susceptible isolates suggests that drug efflux may contribute less to the resistance to certain classes of antibiotics than inactivation of enzymes. A resistance island with a variable composition of resistance determinants interspersed with transposons, integrons, and other mobile genetic elements is a significant contributor to the multidrug-resistant phenotype. A whole-genome sequencing analysis of six closely related clinical isolates of *A. baumannii*, including four from one hospital, revealed an extensive divergence of the resistance genotype that correlated with the observed differences in antimicrobial susceptibility[106]. Resistance genes associated with insertion sequences, plasmids, and a chromosomal resistance gene island all showed certain degrees of variability. The dynamic resistance gene pool suggests the rapid evolution of drug resistance in *A. baumannii*. The whole-genome sequencing of three dominant *A. baumannii* strains in an outbreak concluded that

much of their diversification was mediated by homologous recombination across 20% of their genomes[107]. The differences in genomic contents among different *Acinetobacter* spp. are partly shaped by their distinct ecological niches[108]. This notion is further supported by the variable presence of some genes encoding transcription factors and transporters among clinical isolates and their environmental *Acinetobacter* spp.[105].

RESISTANCE MECHANISMS

Overview

Currently, centain strains of *A. baumannii* is highly resistant to most antibiotics available in clinical practice. A number of resistance mechanisms to many classes of antibiotics are known to exist in *A. baumannii*, including β-lactamases, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and the alteration of target sites[109-111]. Most of these resistance mechanisms can target different classes of antibiotics. However, several different mechanisms can work together to contribute to the resistance to a single class of antibiotics. For example, the resistance mechanisms in CRAB are diverse[112]. In addition to β-lactamases with carbapenem-hydrolyzing activity as a major carbapenem resistance mechanism, which include carbapenem-hydrolyzing class D β-lactamases (CHDLs) and metallo-β-lactamases (MBLs), porins such as CarO[66] and penicillin-binding protein modifications might also be involved in carbapenem resistance[113]. The spread of multidrug-resistance determinants in *A. baumannii* is mostly through plasmid conjugation, transposon acquisition or integron mobilization to gain clusters of genes encoding resistance to several antibiotic families[110]. Furthermore, the functional insertion sequences are important in amplifying antimicrobial resistance and gene plasticity[114-118]. Table 1 shows the various antimicrobial resistance mechanisms of *A. baumannii*. The details are further discussed below.

β-lactamase

Inactivation of β-lactams constitutes an important part of multidrug resistance in *A. baumannii*, especially for β-lactam antibiotic resistance. All four Ambler classes of β-lactamases (*i.e.*, classes A, B, C and D) can be identified in this organism[66]. Although a wide range of class A β-lactamases, including those of temoneira (TEM)[119-121], sulfhydryl variable (SHV)[122], cefotaxime hydrolyzing capabilities (CTX-M)[123,124], guiana extended-spectrum (GES)[115,125], self-transferable plasmid from *E. coli* (SCO)[126], *Pseudomonas* extended resistant (PER)[127-130], vietnam extended-spectrum β-lactamase (VEB)[96,131-133], carbenicillin hydrolyzing β-lactamase (CARB)[134,135] and *K. pneumoniae* carbapenemase (KPC)[136], have been reported in *A. baumannii* (Table 1), they are generally regarded to play a minor role in its resistance phenotype, especially in carbapenem resistance. Some of these enzymes are narrow-spectrum β-lactamases, *e.g.*, TEM-1[119-121], SCO-1[126] and CARB-4[135]; however, a number of these enzymes are still responsible for the hydrolysis of extended-spectrum β-lactams (ESBL). PER-1 was the first ESBL enzyme identified in *A. baumannii*[137], whereas TEM-92 and CARB-10 were the first reported TEM-type[120] and CARB-type[134] ESBLs, respectively. Later, the chromosomally encoded ESBLs SHV-5[122], PER-2[132] and PER-7[129,130] were also described. *A. baumannii* strains carrying the extended spectrum VEB-1 enzyme were first reported in an outbreak in France[131]. GES-11, an integron-associated GES variant, can even confer reduced susceptibility to carbapenems[115,125]. In addition, CTX-M enzymes are transmitted by integrons or plasmids, indicating the potential dissemination in outbreaks between different strains[123, 124]. Finally, KPC-10 was the first KPC β-lactamase to be identified[136].

Class B β-lactamases can confer resistance to the majority of β-lactams because of their broad range, potent carbapenemase activity and resistance to inhibitors[138]. Although MBLs are not the predominant carbapenemases in *A. baumannii*, verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP) and seoul imipenemase (SIM) MBLs have been found contribute to the high-level resistance to carbapenems. The first VIM enzyme was described by Yum in 2002[139]. Thereafter, several other VIM variants, including VIM-1[140-142], VIM-3[143], VIM-4[141,142], and VIM-11[143], were identified in *A. baumannii*. IMP enzymes have also been reported in several Gram-negative bacteria worldwide, including *A. baumannii*. At least nine variants of IMP enzymes have been identified in *A. baumannii*: IMP-1[144], IMP-2[145], IMP-4[146,147], IMP-5[148], IMP-6[149], IMP-8[143], IMP-11[150], IMP-19[150] and IMP-24[143]. SIM-1 is the only SIM enzyme that has been reported in *A. baumannii*[151]. More recently, NDM (new Deli metallo-β-lactamase)-1[152-154] and NDM-2[155] were observed in *A. baumannii*. *bla*$_{NDM-1}$ is integrated in the chromosome within a new transposon structure with two copies of the insertion sequence IS*Aba125* in one clinical strain of *A. baumannii*. Such variability of the genetic environment of *bla*$_{NDM-1}$ likely facilitates its rapid dissemination[153].

The nucleotide sequence of the chromosomal cephalosporinase gene, which encodes an AmpC β-lactamase, in *A. baumannii* was first characterized in a clinical isolate from Spain in 2000[156]. Different isolates of *A. baumannii* have been shown to have almost identical AmpC sequences (no more than two amino-acid substitutions)[157]. A phylogenetic analysis showed that *Acinetobacter ampC* genes are descended from a common ancestor and are more closely related to each other than the *ampC* genes found in other species of bacteria[158]. The class C chromosomal β-lactamase AmpC in *A. baumannii* has a typical cephalosporinase substrate profile[156]. The presence of AmpC β-lactamase plays an important role in β-lactam resistance in *A. baumannii*, and in fact, a high percentage of drug-resistant *A. baumannii* possess *bla*$_{ampc}$[119]. In a study of 23 MDRAB clinical isolates from five proximal hospitals in Taiwan, all isolates had AmpC-type *bla*[77]. The presence of an insertion sequence with a strong promoter upstream of *ampC* in *A. baumannii* clinical isolates has the potential to overexpress AmpC, resulting in high-

Table 1 Antimicrobial resistance mechanisms in *Acinetobacter baumannii*

Resistance mechanism	Class/family	Protein	Ref.
β-lactamases	Class A	TEM-1	[105,119,121]
		TEM-92	[120]
		SHV-5	[122]
		CTX-M-2	[123]
		CTX-M-15	[124]
		GES-11	[115,125]
		GES-12	[115]
		GES-14	[115]
		SCO-1	[126]
		PER-1	[127,128]
		PER-2	[132]
		PER-7	[129,130]
		VEB-1	[96,105,131-133]
		CARB-4	[135]
		CARB-10	[134]
		KPC-10	[136]
	Class B	VIM-1	[140-142]
		VIM-2	[139,143]
		VIM-3	[143]
		VIM-4	[141,142]
		VIM-11	[143]
		IMP-1	[144]
		IMP-2	[145]
		IMP-4	[146,147]
		IMP-5	[148]
		IMP-6	[149]
		IMP-8	[143]
		IMP-11	[150]
		IMP-19	[150]
		IMP-24	[143]
		SIM-1	[151]
		NDM-1	[152-154]
		NDM-2	[155]
	Class C	AmpC	[156-160]
	Class D		
	Narrow-spectrum		
	OXA-3 group	OXA-21	[163]
	OXA-20 group	OXA-37	[164]
	OXA-10 group	OXA-128	[387]
	CHDLs		
	OXA-23 group	OXA-23	[66,92,105,147,167-183]
		OXA-133	[185]
	OXA-24 group	OXA-40/24	[197,201,204]
		OXA-40	[188,200, 202,203]
		OXA-72	[92,205,206]
		OXA-25, OXA-26, OXA-27	[198]
	OXA-51 group	OXA-51	[105,187-190]
		OXA64, OXA-65, OXA-66, OXA-68, OXA-70, OXA-71	[191]
		OXA-69, OXA-75, OXA-76, OXA-77	[186]
		OXA-79, OXA80, OXA-104, OXA106~OXA-112	[194]
		OXA-82, OXA-83, OXA-84	[192,194]
		OXA-86, OXA-87	[193]
		OXA-88, OXA-91, OXA-93, OXA-94, OXA-95, OXA-96	[147]
		OXA-92	[195]
		OXA-113	[122]
	OXA-58 group	OXA-58	[116,118,207,210,211, 21,5,219]
		OXA-96	[147]
		OXA-97	[220]
	Novel groups	OXA-143	[196]
		OXA-182	[221]
		OXA-235	[222]
Efflux pumps	RND	AdeABC	[235,238]
		AdeFGH	[243]
		AdeIJK	[244]
	MFS	TetA	[248]
		CmlA	[225]
		MdfA	[233]
		CraA	[249]
		AmvA	[250]
	MATE	AbeM	[251]
	SMR	AbeS	[252]
AME	AAC	AAC3 (aacC1, aacC2)	[256]
		AAC (6′) (*aacA4*)	[17,253,257-259,261]
	ANT	ANT (2″) (*aadB*)	[256]
		ANT (3″) (*aadA1*)	[17,253,261]
	APH	APH (3′) (*aphA1*)	[255]
		APH (3″)	[253]
Permeability defects		CarO	[263-267]
		47-kDa OMP	[91]
		44-kDa OMP	[91]
		37-kDa OMP	[91]
		33-36-kDa OMP	[269]
		22-33-kDa OMP	[268]
		43-kDa OMP	[271]
		Lipopolysaccharide	[64]
		OmpA	[274]
Alteration of target sites	Change of PBP	PBP2	[276]
	DNA gyrase	GyrA/ParC	[237]
	Ribosomal protection	TetM	[280]
	Dihydrofolate reductase	Dfr or Dhfr	[17,281]
		FolA	[281]
	16S rRNA methylation	ArmA	[253,258,282-286]

TEM: Temoneira; SHV: Sulfhydryl variable; CTX-M: Cefotaxime hydrolyzing capabilities; GES: Guiana extended-spectrum; SCO: Self-transferable plasmid from *E. coli*; PER: *Pseudomonas* extended resistant; VEB: Vietnam extended-spectrum β-lactamase; CARB: Carbenicillin hydrolyzing β-lactamase; KPC: *K. pneumoniae* carbapenemase; VIM: Verona integron-encoded metallo-β-lactamase; IMP: Imipenemase; SIM: Seoul imipenemase; NDM: New Deli metallo-β-lactamase; AmpC: Ampicillin class C β-lactamase; CHDL: Carbapenem-hydrolyzing class D β-lactamase; OXA: Oxacillinase; RND: Resistance-nodulation-division; MFS: Major facilitator superfamily; MATE: Multidrug and toxic compound extrusion; SMR: Small multidrug resistance; Ade: *A. baumannii* multidrug-resistant efflux pump; TetA: Tetracycline resistant *Acinetobacter*; CmlA: Chloramphenicol resistance *Acinetobacter*; MdfA: Multidrug facilitator; CraA: Chloramphenicol resistance *Acinetobacter*; Amva: *A. baumannii* Methyl Viologen and antimicrobial resistance protein; AbeM: *A. baumannii* efflux pump of MATE family; AbeS: *A. baumannii* efflux pump of SMR family; AME: Aminoglycoside-modifying enzyme; AAC: Aminoglycoside acetyltransferases; ANT: Aminoglycoside adenyltransferases; APH: Aminoglycoside phosphotransferases; CarO: Carbapenem-associated outer membrane protein; OMP: Outer membrane protein; PBP: Penicillin binding protein; GyrA/ParC: DNA Gyrase/partitioning of the nucleoid partition; Dhfr: Dihydrofolate reductase; FolA: Folate; ArmA: Armillaria mellea.

level ceftazidime resistance[159,160]. IS*Aba1*-like sequences have been identified immediately upstream of the *bla*$_{ampC}$ gene in ceftazidime-resistant *A. baumannii* isolates but have been shown to be absent in ceftazidime-susceptible *A. baumannii* isolates[157].

Class D β-lactamases were designated OXAs in reference to their preferred substrate oxacillin[161]. Some OXAs are also able to hydrolyze extended-spectrum cephalosporins, and some can even inactivate carbapenems by acting as carbapenemases[66]. At least 121 different variants of class D β-lactamases have been identified at the protein level, and in contrast to other class D β-lactamases, 45 of these variants exhibit carbapenem-hydrolyzing activities[162]. The *bla*$_{oxa}$ genes can be located either on a chromosome or a plasmid and can sometimes be found in integrons[163,164]. Among the four classes of β-lactamases, MBLs and CHDLs are the two main groups of carbapenemases in *A. baumannii*, the latter of which is responsible for the most common type of carbapenem resistance *via* enzymatic degradation[165]. Currently, nine major subgroups of OXA carbapenemases have been identified based on amino acid homologies[166]. Four subgroups of OXA with carbapenemase activity, including the OXA-23, OXA-40/24, OXA-51 and OXA-58 clusters, are prevalent in *A. baumannii*[162,166].

New OXA-type carbapenemases have been frequently discovered since the first clinical isolate of *A. baumannii* with OXA-23 was characterized[66]. The *bla*$_{OXA-23}$ carbapenemase gene has also been disseminated worldwide[167]. The countries that have reported *A. baumannii* with OXA-23 carbapenemase include France[168-170], Germany[171], Bulgaria[172], Romania[173], the United States[105], Colombia[174], Brazil[175], Australia[176], Taiwan[177,178], China[92,179], Korea[180], Singapore[147,181], Italy[182] and Spain[183]. *A. radioresistens* has been proposed as a silent source of *bla*$_{OXA-23}$ for *A. baumannii*[184], and a novel variant, named *bla*$_{OXA-133}$, has been reported by the Asia-Pacific SENTRY surveillance program[185].

OXA-51/69-like β-lactamases are intrinsic chromosomal enzymes in *A. baumannii*[166,186] that emerged as a new subgroup of carbapenemases in MDRAB in 2004[187] and that show increased carbapenemase activity when IS*Aba1* is upstream of the promoter region[188,189]. However, drug export by an efflux pump might be more important in some clinical isolates[190]. A comparative genomics study by Adams *et al*[105] showed that the studied *A. baumannii* strains, including wild-type strains and clinical isolates of MDRAB, all possessed genes belonging to the OXA-51 group. The recently identified OXA-51 group of β-lactamases comprises a novel cluster among the OXA-type carbapenemases, and the cluster includes many variant oxacillinases that have been reported in several studies, including those by Heriter in 2005[186], Brown in 2005[191], Turton in 2006[192], Vahaboglu in 2006[193], Koh in 2007[147], Evans in 2007[194], Naas in 2007[122], Tsakris in 2007[195] and Higgins in 2009[196]. The CHDLs that have been found are listed in Table 1.

The OXA-40/OXA-24 CHDL group is made up of OXA-25, OXA-26, OXA-40, and OXA-72 (an original sequencing error occurred in sequencing OXA-24; it is now known as OXA-40)[166]. These enzymes only differ by a few amino acid substitutions. OXA-40/OXA-24 was originally identified as chromosomally encoded in a carbapenem-resistant *A. baumannii* isolate recovered from Spain[197]. OXA-25, OXA-26, and OXA-27 were later characterized to be associated with carbapenem resistance in clinical isolates of *A. baumannii* from Spain, Belgium and Singapore[198]. Thereafter, the OXA-40/OXA-24 gene in *A. baumannii* was reported in several areas[199], including Spain[188,200,201], Portugal[202] and the United States[203]. The plasmid-mediated *bla*$_{OXA-24}$ gene was noted in the isolates from an outbreak in Spain[204]. Additionally, OXA-72 has been identified in *A. baumannii* isolates from Taiwan[205], China[92] and Croatia[206].

OXA-58 was first identified from an isolate of MDRAB in France[207]. The *bla*$_{OXA-58}$ gene was found to be plasmid borne. Many OXA-58-producing *A. baumannii* isolates were reported worldwide in subsequent years, including isolates in Europe[208-211], Argentina[208], Kuwait[208], the United Kingdom[208], Australia[212], Taiwan[116], the United States[213,214] and China[215]. A number of outbreaks have also been reported in many countries, including Italy[216], Belgium[79], France[217], Turkey[193], Greece[218,219], and the United States[214]. OXA58 can lead to high-level carbapenem resistance in *A. baumannii via* the upstream IS*1008* insertion[116] or the presence of the ISAba825-ISAba3-like hybrid promoter[118]. OXA-97 is a point mutation variant of OXA-58 that shares the same hydrolytic properties and has been recently identified in *A. baumannii* isolates from Tunisia[220]. Another point mutation derivative is OXA-96, which was identified in *A. baumannii* from Singapore[147].

In 2009, a novel CHDL, OXA-143, was identified that shares 88% amino acid identity with OXA-40, 63% identity with OXA-23, and 52% identity with OXA-58[196]. Another novel oxacillinase, OXA-182, was identified in imipenem-nonsusceptible *Acinetobacter* isolates in Korea[221] and showed 93% identity with OXA-143 and 89% identity with OXA-40 based on amino acid sequence alignment. OXA-235, and the amino acid variants OXA-236 and OXA-237, were identified from *A. baumannii* isolates from the United States and Mexico[222]. The deduced amino acid sequences shared an 85% identity with OXA-134, 54 to 57% identities with the acquired OXA-23, OXA-24, OXA-58, and OXA-143, and a 56% identity with the intrinsic OXA-51. Thus, OXA-235, OXA-236 and OXA-237 represent a novel subclass of OXAs. The expression of OXA-235 in *A. baumannii* leads to reduced carbapenem susceptibility, while the cephalosporin minimal inhibition concentrations (MICs) are unaffected.

Multidrug efflux pumps

While multidrug-resistant efflux pumps have been shown to have roles in bacterial pathogenicity[223], the contribution of efflux pumps to bacterial multidrug resistance is often reported[224,225]. Efflux-based mechanisms are responsible for resistance against many different classes of antibiotics, including tigecycline resistance[226,227] or imipenem resistance[190] in *A. baumannii*. Furthermore, the

linear relationship between the log-transformed expression values of the AdeABC efflux pump genes and the log-transformed MIC values is statistically significant, indicating that overexpression of the AdeABC efflux pump is a prevalent mechanism for decreased susceptibility to tigecycline[228]. The importance of efflux pumps in multidrug resistance in *A. baumannii* is supported by the fact that the presence of efflux pump inhibitors, such as 1-(1-naphthylmethyl)-piperazine[229,230], phenyl-arginine-β-naphthylamide[231,232], or carbonyl cyanide 3-chlorophenylhydrazone[232], can reverse the resistance pattern.

Four categories of efflux pumps, including the resistance-nodulation-division (RND) superfamily, the major facilitator superfamily (MFS), the multidrug and toxic compound extrusion (MATE) family and the small multidrug resistance (SMR) family transporters, have been reported to be related to antimicrobial resistance in *A. baumannii*[233,234]. Of these different pumps, the RND and MFS transporters are mentioned most often. AdeABC, a RND-type efflux pump with a three-component structure, is not only associated with aminoglycoside resistance[235] but is also associated with decreasing susceptibility to several antimicrobials, including tigecycline[226]. Differences in the expression of *adeABC* were shown to contribute to both inter- and intra-clone variation in tigecycline MICs in a study of *A. baumannii* epidemic clones[236]. Both the increase in tigecycline resistance during therapy[236] and the decrease in susceptibility to non-fluoroquinolone antibiotics during an outbreak[237] are mediated by the up-regulation of AdeABC in *A. baumannii*. The AdeABC pump in wild *A. baumannii* is cryptic due to stringent control by the AdeRS two-component system[238]. Point mutations in AdeS and AdeR or a truncation of AdeS due to an IS*Aba1* insertion may be related to the overexpression of AdeABC, which leads to multidrug resistance[238,239]. However, the existence of tigecycline-nonsusceptible and *adeB*-overexpressing *A. baumannii* clinical isolates without known *adeRS* mutations[240] and the low expression of *adeABC* in a clinical strain of *A. baumannii* with the IS*Aba1* insertion in the *adeRS* operon[239] suggest that the regulation of *adeABC* gene expression is complex. Additionally, the cell density-dependent expression of *adeB* suggests the presence of global regulatory mechanisms for the expression of this gene in *A. baumannii*[241]. BaeSR, which functions as an envelope stress response system to external stimuli, is proposed to influence the transcription of *adeAB* and thus tigecycline susceptibility in *A. baumannii* by functioning as a regulator of global transcription[242].

In addition to the AdeABC efflux pump, the inactivation of other RND-type efflux pumps, including AdeFGH[243] and AdeIJK[232,244,245], demonstrates their contribution to multidrug resistance in *A. baumannii*. The AdeABC and AdeIJK efflux systems can contribute synergistically to tigecycline resistance[244]. An open reading frame encoding a LysR-type transcriptional regulator, named *adeL*, is located upstream of the *adeFGH* operon and is responsible for the overexpression of AdeFGH[243], whereas the expression of AdeIJK in *Acinetobacter baumannii* is regulated by AdeN, a TetR-Type regulator[246]. Although the RND efflux pump AdeDE was initially identified in *Acinetobacter* genomic group 3[247], *adeE* was later found to coexist with *adeB* in some clinical isolates of *A. baumannii*[245].

A number of MFS efflux pumps, including TetA[248], CmlA[225], MdfA[233], CraA[249] and AmvA[250], that mediate resistance to different types of antibiotics in *A. baumannii* have been characterized. AbeM, a H-coupled pump that belongs to the MATE family[251], was reported to be present in the clinical isolates of *A. baumannii* in several studies[77,232,245] and to confer resistance to fluoroquinolones or imipenem in *A. baumannii*. *A. baumannii* with a mutant AbeS SMR pump exhibits erythromycin and chloramphenicol resistance[252].

Aminoglycoside-modifying enzymes

Aminoglycoside-modifying enzymes (AMEs) are the principal mode of resistance to aminoglycosides. This resistance is primarily mediated by three classes of enzymes, including acetyltransferases, adenyltransferases and phosphotransferases, that typically reside on transposable elements; these enzymes chemically modify aminoglycosides[253]. The coding genes for these enzymes can be transferred among different bacterial types through plasmids, transposons, integrons, and natural transformation or transduction[254]. A phenotypic analysis of aminoglycoside resistance profiles indicated that many isolates could produce a combination of aminoglycoside-modifying enzymes[255,256]. The co-carrying of four AME genes, including a novel AME gene *aac(6')-Ib*, was reported in a PDRAB strain from China[257]. The identification of MDRAB isolates harboring genes for the *bla*$_{\text{OXA-23}}$-like genes, AME (*aac(6')-Ib*) and the 16S rRNA methylase (*armA*) implicates AMEs in multidrug resistance[258].

Different types of AMEs have been reported in *A. baumannii*. Amikacin resistance has been reported to be associated with a gene encoding APH(3')-VI phosphotransferase[255]. Furthermore, AME *aac(6')-Iad* plays an important role in amikacin resistance in *Acinetobacter spp.* in Japan[259]. Of the 106 MDRAB isolates identified in one study, 95% possessed at least one type of AME, including *aacA4*, *aacC1*, *aacC2*, *aadB*, *aadA1*, *aphA1* and *aphA6*[256]. In another study in Greece, all of the collected *A. baumannii* strains contained AMEs, which were either *aac(6')-Ib* or *aac(6')-Ih*[260]. Class I integrons containing the gene cassettes *aacA4-catB8-aadA1*, *dhfrXII-orfF-aadA2*, or *aacC1-orfP-orfP-orfQ-aadA1* have been proposed to be associated with the horizontal transfer of diversified aminoglycoside-resistant genes among clinical isolates of *A. baumannii*[17,256,261].

Permeability defects

Porins, which perform multiple functions in membranes, are proteins that can form channels to allow the transport of molecules across lipid bilayer membranes[233]. These outer membrane proteins not only influence the virulence of *A. baumannii*, *e.g.*, through Omp38-induced epithelial cell apoptosis[59], biofilm formation related to OmpA[262],

OmpA-dependent host cell death[263], and attenuated virulence by the decreased expression of genes encoding CarO- and OprD-like proteins[263], but also play a significant role in the mechanisms of resistance. For example, the loss of a 29 kDa outer-membrane protein, which was later shown to be CarO, contributes to imipenem resistance[263-267]. Several other studies have also identified a number of OMPs involved in the carbapenem resistance of *A. baumannii*. A reduction in the expression of two porins of 22 and 33 kDa was involved in the carbapenem resistance of *A. baumannii* strains in an outbreak in Spain[268]. In one study, CRAB isolates found in New York had reduced expression of the 47-, 44-, and 37-kDa outer-membrane proteins[91], while in other studies, a 33- to 36-kDa OMP was also shown to be associated with carbapenem resistance in *A. baumannii*[269,270]. A 43-kDa OMP, belonging to the OprD family, has been identified as a basic amino acid and imipenem porin through electrophoresis and MALDI-MS analyses[271].

In the presence of OXA carbapenemases, including OXA-51-like or OXA-23-like enzymes, the loss of the 29-kDa outer-membrane protein is associated with a higher imipenem MIC in *A. baumannii*[272,273]. Moreover, a novel insertion sequence, IS*Aba10*, inserted into IS*Aba1* adjacent to the *bla*$_{\text{OXA-23}}$ gene, can disrupt the outer-membrane protein gene *carO* in *A. baumannii*[180]. The loss of lipopolysaccharide (LPS) from the outer membrane, resulting in a decrease in membrane integrity, occurred in a colistin-resistant clinical isolate of *A. baumannii* in Australia[64]. Disruption of the *ompA* gene can lead to decreases in the MICs of chloramphenicol, aztreonam, and nalidixic acid[274].

Alteration of target sites

Changes in penicillin-binding proteins (PBPs), mutations of DNA gyrase, ribosomal protection by the TetM protein and the involvement of dihydrofolate reductase in trimethoprim resistance all occur *via* mechanisms that alter the target sites for antibiotics[275]. Imipenem resistance has been associated with the overexpression of certain PBPs with a low affinity for imipenem in the absence of other known resistance mechanisms[276]. While an insertion sequence disrupting the gene encoding PBP6b has been identified in an endemic carbapenem-resistant clone, its role must be further evaluated[277]. Furthermore, mutations in DNA gyrase gene *gyrA* and *parC*, which encode topoisomerase Ⅳ, have been reported in an *A. baumannii* outbreak investigation[237]. The *gyrA* mutation at Ser-83 was shown to be associated with quinolone resistance in epidemiologically unrelated isolates of *A. baumannii*[278]. While *tetA* and *tetB* genes are well recognized for their role in tetracycline resistance in *A. baumannii* through efflux pumps[225,279], *tetM* is proposed to be another resistance mechanism that acts through ribosomal protection[280]. Trimethoprim resistance through dihydrofolate reductase in *A. baumannii* is similar to that of other bacteria. Plasmids containing *folA* genes and integrons harboring *dfr* or *dhfr* genes in *A. baumannii* have been found[17,279,281]. Recently, the coexistence of the 16S rRNA methylase *armA* gene and genes encoding OXA carbapenemases were reported in many countries, including China[282], South Korea[253,283], India[284], Italy[285], Japan[286], and Yemen[258], indicating the contribution of the *armA* gene to the multidrug resistance of MDRAB.

Roles of integrons

The horizontal transfer of resistance genes is a successful mechanism for the transmission and dissemination of multiple drug resistance determinants among bacterial pathogens[287]. Integrons, which are located on either bacterial chromosomes or plasmids, are assembly platforms that incorporate exogenous ORFs by site-specific recombination and convert them to functional genes by ensuring their correct expression[288]. Integrons share common features: a gene encoding an integrase, a specific recombination site that is recognized by the integrase and into which the cassettes are inserted, and a promoter that directs the transcription of the cassette-encoded genes. Currently, there are four classes of integrons, and class 1 integrons are the most common in bacteria[289].

The role of integrons in the development of multidrug resistance relies on their unique capacity to cluster and express drug resistance genes[287]. Many studies regarding integrons harboring different types of resistance genes have been reported worldwide in recent decades. Class I integrons were detected in 52.8% of *A. baumannii* strains in the Nanjing area of China in 2007[290], whereas an epidemic, class 1 integron-carrying MDRAB clone was found to be widespread in Taiwan in the same year[291]. Four different integron structures were detected in 84% of all collected isolates of *A. baumannii* in a Spanish study[255]. However, while no clear antibiogram differences could be associated with the presence or absence of integron structures in the Spanish study, other reports have suggested that integrons play a major role in multidrug resistance in *A. baumannii*[261,291,292]. Additionally, epidemic strains of *A. baumannii* have been found to contain significantly more integrons than non-epidemic strains[293]. Therefore, integrons are regarded as useful markers for epidemic strains of *A. baumannii*, and their typing can provide valuable information for epidemiological studies[294,295].

A study performed in Italy found that 44% of the epidemiologically unrelated *A. baumannii* isolates collected over an 11-year period were integron-positive[296]. Most integron-positive strains carried the same array of cassettes, despite their notable genetic diversity that was identified through a ribotyping analysis, implying that horizontal transfer of the entire integron structure or an ancient acquisition occurred. Additionally, while the same integron can be present in unrelated strains[17], related strains can also have different integrons[297].

Although different relationships exist among different classes of antibiotics and integrons[298,299], most studies have emphasized the association of integrons with cassette genes and aminoglycoside resistance[261]. The diversity of the genes encoding AMEs and their association with class 1 integrons was observed in a study involving

three pan-European clones of *A. baumannii*[256]. Six different class 1 integron variable regions were detected in 74% of the collected strains. Furthermore, Huang *et al*[291] collected 283 MDRAB isolates from three medical centers in Taiwan from 1996 to 2004 and found seven types of gene cassettes, most of which contained AMEs, including *aacA4*, *aacC1*, *aac(6')-II*, *aadA1*, *aadA2*, *aadA4* and *aadDA1*.

Variable CHDL genes, including *bla*$_{OXA-3}$[292], *bla*$_{OXA-10}$[96,290], *bla*$_{OXA-20}$[19,292,296], *bla*$_{OXA-21}$[297], and *bla*$_{OXA-37}$, have been reported in integrons[164,297]. Integron-associated imipenem resistance in *A. baumannii* has also been documented[300]. Genes encoding carbapenemases, such as MBLs *bla*$_{VIM}$, *bla*$_{IMP}$ and *bla*$_{SIM}$, have been found in integrons. *bla*$_{VIM-1}$-carrying integrons[140] and *bla*$_{VIM-2}$-carrying integrons[139] have been noted in Greece and Korea, respectively. In Taiwan, integron-mediated gene spreading has been demonstrated hospitals[301], especially in a unit with high antibiotic selective pressure[302]. *bla*$_{VIM-11}$-carrying integrons have also been identified in MDRAB isolates, and this MBL gene has been postulated to spread among *Pseudomonas aeruginosa* and *A. baumannii* strains[143,291]. Other reported MBLs include *bla*$_{IMP-1}$[303], *bla*$_{IMP-2}$[145], *bla*$_{IMP-4}$[146,147], *bla*$_{IMP-5}$[148], *bla*$_{IMP-8}$[291] and *bla*$_{SIM-1}$[151]. The genes for chloramphenicol resistance in the integrons of *A. baumannii* are *catB2*[135], *catB3*[146,147,151] and *catB8*[294,304].

CLINICAL IMPACT OF ANTIMICROBIAL RESISTANCE

The clinical impact of *A. baumannii* infections has been a matter of debate[2]. A high mortality rate in immunocompromised hosts with *A. baumannii* infections had been attributed to the patients' underlying diseases rather than to the infections. One Spanish study concluded that there were no differences in mortality among patients with ventilator-associated pneumonia (VAP) caused by imipenem-resistant or imipenem-susceptible *A. baumannii* or by other pathogens[305]. However, other related studies suggest that *A. baumannii* infection itself has a profound influence on high mortality or prolonged length of stay (LOS)[306]. Falagas suggested that the mortality attributed to *A. baumannii* infections should no longer be a controversial issue[307] based on six relevant case-control studies[308-313].

Several previous surveillance[314-317] studies have demonstrated that increasing antimicrobial resistance, especially multidrug resistance, has become a major issue in *A. baumannii* strains in recent years. Whether multidrug resistance is a risk factor for high mortality in *A. baumannii* infections has been a controversial issue. A few studies suggested that MDRAB-related pneumonia or bacteremia is a signal of disease severity and is not related to prolonged LOS or increased mortality[318,319], but more recent studies have shown that MDRAB infections lead to higher mortality. The acquisition of MDRAB was shown to be an independent risk factor for mortality in a burn center in Singapore[320]. A multicenter retrospective study in Taiwan also showed that patients with CRAB infections have a higher mortality rate than those with carbapenem-susceptible *A. baumannii* infections[321], which is consistent with the results of several previous studies[309-311,313,322]. The high impact of imipenem resistance on the mortality rate of patients with *Acinetobacter* bacteremia is chiefly attributable to discordant antimicrobial therapy[311]. Moreover, patients with MDRAB infections have increased hospital and ICU LOS compared to patients with susceptible *A. baumannii* infections and uninfected patients[308]. A mini review of this issue indicated that blood stream infections and nosocomial ICU infections caused by carbapenem-resistant *Acinetobacter* spp. are associated with increased rates of mortality, whereas other types of infections have not clearly been shown to be associated with higher mortality rates but are associated with increased LOSs and hospital costs[323].

STRATEGIES TO COMBAT THE DISSEMINATION OF ANTIMICROBIAL RESISTANCE

The development of new antibiotics against MDRAB and the implementation of infection control measures are regarded as two methods to aid in controlling the increasing problem of *A. baumannii* infections[307]. When GlaxoSmithKline shared the challenges and difficulties in screening for new classes of antimicrobial agents over a 7-year period, the authors concluded that the pipeline of novel-mechanism antibacterials is still empty and will remain so for a considerable period[324]. Therefore, the importance of following the Association of Professionals in Infection Control and Epidemiology's (APIC) 2010 guide to the elimination of MDRAB transmission in health care settings cannot be overemphasized[325]. This guide includes MDRAB risk assessment and infection surveillance, strict adherence to hand hygiene protocols, implementation of standard and transmission-based precautions, environmental decontamination, outbreak recognition and control, and antibiotic stewardship.

Gastrointestinal or skin colonization of *A. baumannii* develops soon after the pathogen is first isolated from a clinical site[326]. The finding of multidrug-resistant colonized strains compared with susceptible clinical strains without apparent relation to antibiotic use implies that a new onset of MDRAB colonization may not be identified without surveillance. Additionally, the increasing occurrence of multidrug-resistant strains among seriously ill patients emphasizes the importance of continued surveillance as a critical component of any program aimed at preventing and controlling antimicrobial resistance[315]. Environmental contamination, airborne transmission, patient transfer, and cross-contamination are regarded as key factors in causing *A. baumannii* epidemics[327], and clonal expansion has been shown to play a major role in the increase of MDRAB in hospitals[328]. Therefore, barrier infection control measures are necessary to prevent the nosocomial spread of MDRAB[326]. One outbreak

Table 2 Antimicrobial treatment for MDRAB infections

Regimen	Pathogen	Diseases	Outcome[1]	Comparator	Ref.
CST + RIF	XDRAB	HAP VAP BSI cIAI	The same in CR (mortality) Better in MR	CST	[367]
CST + RIF	CRAB	VAP	The same in CR + MR	CST	[366]
CST + IPM CST + SAM CST + others	XDRAB	BSI	Better in CR (mortality) + MR	CST	[369]
CST + SUL	MDRAB	VAP	The same in CR + MR	CST	[341]
TGC based	MDRAB	Pneumonia	Higher mortality	CST based	[349]
TGC based	MDRAB	HAIs	The same in mortality[2] Better in MR	IPM + SAM	[352]
CT	MDRAB	Infections	The same in mortality	MT	[374]

[1]"The same" means no significant difference between comparator groups, and "Better" means a significant difference exists between comparator groups; [2]Has a statistically significant favorable outcome. MDRAB: Multidrug-resistant *A. baumannii*; CST: Colistin; IPM: Imipenem; RIF: Rifampicin; SUL: Sulbactam; SAM: Ampicillin/sulbactam; TGC: Tigecycline; HAP: Hospital-associated pneumonia; VAP: Ventilator-associated pneumonia; BSI: Blood stream infection; cIAI: Complicated intra-abdominal infection; HAIs: Healthcare-associated infections; CR: Clinical response; MR: Microbiological response; CT: Combination therapy; MT: Monotherapy.

reported in an ICU in a Greek hospital ceased after the implementation of hygienic measures, complete cleaning and complete disinfection in the ICU[329]. However, cross-infection with *A. baumannii* among patients still occurred, despite the implementation of stringent infection control measures, in a previously reported outbreak; thus, temporary closure of the surgical ward for disinfection was necessary to control the outbreak[330].

Environmental contamination plays an important role in the transmission of MDRAB. One outbreak investigation found that the affected patients had a higher risk of harboring *A. baumannii* after blood transfusion, hydrotherapy or extended use of a respirator, which was possible through the contamination of healthcare personnel and the environment. Another *A. baumannii* outbreak investigation in a surgical ICU at a teaching hospital in Taiwan showed extensive amounts of environmental contamination, including the contamination of bed rails, bedside tables, sinks, ventilator and infusion pump surfaces, and water for nasogastric feeding and ventilator rinsing. Hence, intensified infection prevention control (IPC) measures are needed to terminate an outbreak. The IPC measures include: (1) implementation of enhanced contact isolation precautions; (2) active surveillance cultures; (3) daily environmental cleaning with detergents and phenolic agents; (4) an up-to-date education program for all healthcare workers; and (5) delivery of real-time feedback to healthcare workers regarding IPC compliance[331], which has minimized the spread of colistin-resistant *A. baumannii*. Furthermore, the infection control bundle resulted in a significant reduction in the incidence of nosocomial *A. baumannii* in one burn unit and prevented further outbreaks of this organism, with an 88.8% decrease during the intervention period[332].

Imipenem has been proven to be a strong inducer of multidrug resistance in *A. baumannii*[333]. Many *A. baumannii* isolates exhibit imipenem resistance, which is strongly associated with the prior use of carbapenems[334]. Because of the high mortality rate associated with *A. baumannii* infection, strategies to slow down the emergence of MDRAB in clinical practice by optimizing antimicrobial therapy are necessary. Therefore, antimicrobial stewardship is mandatory in an infection prevention program to prevent the emergence and transmission of MDRAB in health care facilities[325].

ANTIMICROBIAL THERAPY

Carbapenems, including imipenem or meropenem, have been regarded as effective antimicrobial agents to treat *A. baumannii* infections[314,335]. With many studies reporting increasingly high rates of CRAB in clinical isolates[75,76,90], other classes of antibiotics or combination therapies are urgently needed. Because the choices of antimicrobial treatment for MDRAB are severely limited by resistance, there are only a few effective options available, including polymyxins and tigecyclines[336]. Furthermore, the appearance of PDRAB, which is resistant to all available antibiotics, including polymyxin, implies that more efforts should be devoted to investigating the treatment options for this superbug[27]. Combination therapies with imipenem/sulbactam, colistin/rifampicin, colistin/sulbactam, colistin/tigecycline, colistin/imipenem or meropenem and colistin/teicoplanin have been studied and proposed as possible choices. The recently published reports on the treatment of MDRAB are summarized in Table 2.

Sulbactam

While ampicillin/sulbactam has been shown to be effective in treating blood stream infections caused by MDRAB[337], a later meta-analysis revealed that sulbactam-based therapy is not superior to other therapeutic approaches, including colistin, cephalosporins, antipseudomonas penicillins, fluoroquinolones, minocycline/doxycycline, aminoglycosides, tigecycline, polymyxin, imipenem/cilastatin, and combination therapies[338]. Although sulbactam-based therapy failed to prove its superiority to other regimens for the treatment of *A. baumannii* in-

fections, a case of skin and soft tissue infection caused by CRAB that was treated successfully with ampicillin/sulbactam and meropenem combination[339] raises the possibility of ampicillin/sulbactam as a component of combination therapy against CRAB. The combination of ampicillin/sulbactam with a carbapenem for treating MDRAB bacteremia has been shown to be associated with a better outcome[340], but such beneficial effects were not observed for MDRAB VAP[341].

Tigecycline-based therapy

In 2004, tigecycline was reported to have a good *in vitro* bacteriostatic effect against *A. baumannii*, including strains resistant to imipenem[342]. Another *in vitro* study using a time-kill assay demonstrated the potential role of tigecycline in the treatment of *A. baumannii* and proposed that doxycycline could be a suitable and cost-effective option in some instances[343]. Tigecycline efficacy was shown to correlate well with the free concentration-time curve of MIC in a murine *Acinetobacter* spp. model[344]. Additionally, several cases affiliated with severe infections by MDRAB were successfully treated with tigecycline in terms of their clinical and microbiological outcomes[345].

With its increasing use, the limitations and adverse aspects of tigecycline in treating MDRAB infections have begun to be realized. Tigecycline was less effective than imipenem in the treatment of pneumonia caused by non-IRAB strains in a murine pneumonia model[346]. In a study consisting of 34 patients with MDRAB infections, the mortality rate reached up to 41%. The authors found that the correlation of clinical and microbiological outcomes was poor and concluded that tigecycline had excellent *in vitro* activity against MDRAB, but its clinical efficacy was still uncertain[336]. One of the possible causes for the discrepancy of treatment outcomes may be variable tigecycline MICs. MIC determination for tigecycline before treatment, with the broth dilution method being favored[347], might increase clinical success[345]. *A. baumannii* isolates with tigecycline MICs of $\geqslant$ 2 mg/L were associated with higher mortality rates; thus, treatment with β-lactams or carbapenems instead of with tigecycline is preferred[348]. This notion was further supported in a matched cohort study in Taiwan that dealt with the effectiveness of tigecycline-based versus colistin-based therapy for the treatment of pneumonia caused by MDRAB[349]. The excess mortality rate of 16.7% in the tigecycline-based group compared with the colistin-based group was mostly attributed to subjects with MIC > 2 μg/mL.

In a meta-analysis of the efficacy and safety of tigecycline, clinical failure, superinfection and adverse events were more frequent with the use of tigecycline[350]. The authors suggested that physicians should avoid tigecycline monotherapy for the treatment of severe infections caused by MDRAB and that they should use it as a last-resort antibiotic. There was no antagonism found when tigecycline was used with other antimicrobials possessing activities against Gram-negative bacteria[351]. However, tigecycline-based therapy for MDRAB infections is not satisfactory. In a study of 266 patients with healthcare-associated MDRAB infections, the mortality rate was not significantly different between those receiving tigecycline-based therapy and those receiving non-tigecycline therapy[352].

While tigecycline has an expanded spectrum of antibacterial activity and a synergic effect with some classes of antibiotics, such as amikacin[353], earlier studies have shown that tigecycline resistance in *A. baumannii* has emerged[354] and is associated with multidrug efflux systems, especially overexpression of the *adeABC* pump[226,227]. The increased expression of the *adeABC* operon can be found in clinical isolates of *A. baumannii* post-tigecycline therapy[236,355]. High resistance rates and high MICs of tigecycline in multiple clones of MDRAB were noted in a medical center in Israel[356]. This phenomenon led to concern regarding the use of tigecycline as one of the few treatment choices for infections caused by MDRAB.

Colistin-based therapy

Colistin has been described as a last resort for the treatment of MDRAB[357], and this drug is often used in combination therapy. In a report on the clonal spread of MDRAB in eastern Taiwan, antibiotic susceptibility testing showed that 10.4%, 47.8% and 45.5% of MDRAB isolates were resistant to colistin, rifampicin, and tigecycline, respectively, implying that colistin was the only effective antimicrobial agent in that area for treating MDRAB[358]. In addition to its intravenous injection for MDRAB infections, colistin can be given *via* intraventricular and intrathecal routes for meningitis[359] and *via* nebulization for pneumonia[360,361].

Unfortunately, colistin-resistant *A. baumannii* strains have been reported all over the world[357] and are attributed to the loss of lipopolysaccharide[64] or/and phosphoethanolamine modification of lipid A mediated by the PmrAB two-component system[362,363]. Because colistin monotherapy is unable to curb the appearance of resistance, colistin-based combination therapy might be the optimal antimicrobial strategy. Colistin combined with different classes of antibiotics, including tigecycline, cefoperazone/sulbactam or piperacillin/tazobactam, revealed synergistic effects in some CRAB strains[364]. Time-kill assays have also shown that colistin/meropenem, colistin/rifampicin, and colistin/minocycline are synergistic *in vitro* against XDRAB strains[365]. The beneficial effects of colistin and rifampicin combination for patients with VAP caused by CRAB have been documented in terms of clinical and microbiological outcomes[366]. However, another multi-center, randomized clinical trial concluded that 30-d mortality was not reduced by the addition of rifampicin to colistin in serious XDRAB infections[367]. Additionally, such a regimen might be hindered by a high level of rifampicin resistance in *A. baumannii*[368]. Treatment with combination therapy, including colistin/carbapenem and colistin/sulbactam, for XDRAB blood stream infections led to higher microbiological eradication and lower mortality rates in comparison with the colistin monotherapy group[369]. The combination therapy

of colistin and tigecycline has also been proposed as a reasonable treatment of choice for XDRAB pneumonia, especially in the first 48 h, in a rat lung model[370]. Interestingly, a significant synergy has been observed for the combination of colistin and teicoplanin against MDRAB *in vitro*[371]. Telavancin, a similar lipoglycopeptide of teicoplanin, has been shown to be efficacious *in vivo* when used in colistin combination therapy in a *Galleria mellonella* model of *A. baumannii* infection[372].

Other antimicrobial therapies

Doripenem, a novel broad-spectrum carbapenem, has displayed *in vitro* synergistic activity with tigecycline, colistin and amikacin against MDRAB strains with doripenem resistance[373]. One recent prospective, observational Spanish study did not support an association of combination therapy with reduced mortality in MDRAB infections[374]. Overall, the choice of combination therapy should take several key factors into consideration, including the antimicrobial resistance phenotype, resistance mechanisms, and MIC[375].

FUTURE PERSPECTIVES

One of the difficulties encountered in understanding the antimicrobial resistance mechanisms of *A. baumannii* lies in the complexity of the involved genes. A DNA microarray, the Check-MDR CT102 microarray, has proven useful in detecting TEM, SHV and CTX-M extended-spectrum β-lactamases and KPC, OXA-48, VIM, IMP, and NDM-1 carbapenemases in some *Enterobacteriaceae* and glucose non-fermentative bacteria, including *A. baumannii*, with 100% sensitivity and specificity for most of the tested genes[376]. The detection of plasmid-mediated cephalosporinases, including CMY-2-like, DHA, FOX, ACC-1, ACT/MIR and CMY-1-like/MOX, was also possible using this assay, suggesting that this DNA array is a powerful high-throughput tool for most common resistance gene identifications and provides a platform for epidemiological or infection-control studies[377].

Bacteria develop resistance to new classes of antibiotics very quickly, and bacteria may even be resistant to new classes of antibiotics before they are introduced to clinical use[378]. Hence, antimicrobial peptides (AMPs) may be another option due to the rare appearance of resistance to AMPs in addition to their antimicrobial and anti-inflammatory effects[379]. AMPs are an important component of host defenses against invading pathogens[380]. They are small, cationic and amphipathic peptides of variable length, sequence and structure. Thus far, more than 750 different AMPs have been identified in various organisms ranging from plants to animals, including humans, most of which exhibit broad-spectrum activity against a wide range of microorganisms by disrupting the plasma membrane and causing cell lysis. Three classes of AMPs, including defensins, cathelicidins, and histatins, have been found in humans[379]. The cathelicidin family is currently limited to a single gene, CAMP. LL-37, which begins with two leucine residues and consists of 37 amino acids, was the first mature peptide isolated from *CAMP* gene products[381].

While only a few studies regarding the use of AMPs in *A. baumannii* have been reported, AMPs might be a potential therapeutic alternative to antibiotics. This hypothesis is supported by the conclusion reached from a study of an LPS-deficient, colistin-resistant *A. baumannii* strain, which showed reduced viability even at a low concentration of LL-37[382]. The human antimicrobial peptide LL-37 and its fragments KS-30 and KR-20 have been shown to have significant antimicrobial activity against clinical isolates of MDRAB, of which the KS-30 fragment exhibits the highest bactericidal ability[383]. Moreover, the prevention of biofilm formation *in vitro* by LL-37, KS-30 and KR-20 adds significance to their efficacy. We predict that AMPs, specifically LL-37, will be promising targets in future research on therapeutics against MDRAB infections.

Because marketing a new antimicrobial is extremely difficult and because bacteria quickly adapt to so-called magic bullets, understanding the interplay between a pathogen such as *A. baumannii* and its hosts may provide another possible solution in the war against bacteria. The microbes that exist in the human body are collectively known as the human microbiota, and this remarkably complex and poorly understood group of communities has an enormous impact on humans[384]. The Human Microbiome Project, funded by the National Institutes of Health, aims to develop tools and databases for the research community to study the role of these microbes in human health and disease. One of the tasks the NIH has set itself is to develop a catalog of the microbial genome sequences of reference strains[385]. For example, the microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease has been documented[386]. More advances in understanding the pathogenesis of *A. baumannii* using the databases of the Human Microbiome Project can be anticipated.

In conclusion, we hope that this review will aid in understanding the relevant studies regarding the antimicrobial resistance of *A. baumannii* as well as the currently available treatment options for the infections that this pathogen cause, thereby leading to new strategies to combat *A. baumannii*.

REFERENCES

1 **Van Looveren M**, Goossens H. Antimicrobial resistance of Acinetobacter spp. in Europe. *Clin Microbiol Infect* 2004; **10**: 684-704 [PMID: 15301671 DOI: 10.1111/j.1469-0691.2004.00942.x]

2 **Visca P**, Seifert H, Towner KJ. Acinetobacter infection--an emerging threat to human health. *IUBMB Life* 2011; **63**: 1048-1054 [PMID: 22006724 DOI: 10.1002/iub.534]

3 **Gerner-Smidt P**, Tjernberg I, Ursing J. Reliability of phenotypic tests for identification of Acinetobacter species. *J Clin Microbiol* 1991; **29**: 277-282 [PMID: 2007635]

4 **Bergogne-Bérézin E**, Towner KJ. Acinetobacter spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. *Clin Microbiol Rev* 1996; **9**: 148-165 [PMID: 8964033]

5 **Dijkshoorn L**, Aucken H, Gerner-Smidt P, Janssen P, Kaufmann ME, Garaizar J, Ursing J, Pitt TL. Comparison of outbreak and nonoutbreak Acinetobacter baumannii strains by genotypic and phenotypic methods. *J Clin Microbiol* 1996; **34**: 1519-1525 [PMID: 8735109]

6 **Houang ET**, Chu YW, Chu KY, Ng KC, Leung CM, Cheng AF. Significance of genomic DNA group delineation in comparative studies of antimicrobial susceptibility of Acinetobacter spp. *Antimicrob Agents Chemother* 2003; **47**: 1472-1475 [PMID: 12654697 DOI: 10.1128/aac.47.4.1472-1475.2003]

7 **Lee JH**, Choi CH, Kang HY, Lee JY, Kim J, Lee YC, Seol SY, Cho DT, Kim KW, Song do Y, Lee JC. Differences in phenotypic and genotypic traits against antimicrobial agents between Acinetobacter baumannii and Acinetobacter genomic species 13TU. *J Antimicrob Chemother* 2007; **59**: 633-639 [PMID: 17339277 DOI: 10.1093/jac/dkm007]

8 **Koeleman JG**, Stoof J, Biesmans DJ, Savelkoul PH, Vandenbroucke-Grauls CM. Comparison of amplified ribosomal DNA restriction analysis, random amplified polymorphic DNA analysis, and amplified fragment length polymorphism fingerprinting for identification of Acinetobacter genomic species and typing of Acinetobacter baumannii. *J Clin Microbiol* 1998; **36**: 2522-2529 [PMID: 9705386]

9 **Chang HC**, Wei YF, Dijkshoorn L, Vaneechoutte M, Tang CT, Chang TC. Species-level identification of isolates of the Acinetobacter calcoaceticus-Acinetobacter baumannii complex by sequence analysis of the 16S-23S rRNA gene spacer region. *J Clin Microbiol* 2005; **43**: 1632-1639 [PMID: 15814977 DOI: 10.1128/JCM.43.4.1632-1639.2005]

10 **La Scola B**, Gundi VA, Khamis A, Raoult D. Sequencing of the rpoB gene and flanking spacers for molecular identification of Acinetobacter species. *J Clin Microbiol* 2006; **44**: 827-832 [PMID: 16517861 DOI: 10.1128/JCM.44.3.827-832.2006]

11 **Bou G**, Cerveró G, Domínguez MA, Quereda C, Martínez-Beltrán J. PCR-based DNA fingerprinting (REP-PCR, AP-PCR) and pulsed-field gel electrophoresis characterization of a nosocomial outbreak caused by imipenem- and meropenem-resistant Acinetobacter baumannii. *Clin Microbiol Infect* 2000; **6**: 635-643 [PMID: 11284921]

12 **Misbah S**, AbuBakar S, Hassan H, Hanifah YA, Yusof MY. Antibiotic susceptibility and REP-PCR fingerprints of Acinetobacter spp. isolated from a hospital ten years apart. *J Hosp Infect* 2004; **58**: 254-261 [PMID: 15564001 DOI: 10.1016/j.jhin.2004.07.007]

13 **Huys G**, Cnockaert M, Nemec A, Dijkshoorn L, Brisse S, Vaneechoutte M, Swings J. Repetitive-DNA-element PCR fingerprinting and antibiotic resistance of pan-European multi-resistant Acinetobacter baumannii clone III strains. *J Med Microbiol* 2005; **54**: 851-856 [PMID: 16091436 DOI: 10.1099/jmm.0.45986-0]

14 **Higgins PG**, Hujer AM, Hujer KM, Bonomo RA, Seifert H. Interlaboratory reproducibility of DiversiLab rep-PCR typing and clustering of Acinetobacter baumannii isolates. *J Med Microbiol* 2012; **61**: 137-141 [PMID: 21903821 DOI: 10.1099/jmm.0.036046-0]

15 **Saeed S**, Fakih MG, Riederer K, Shah AR, Khatib R. Inter-institutional and intrainstitutional transmission of a strain of Acinetobacter baumannii detected by molecular analysis: comparison of pulsed-field gel electrophoresis and repetitive sequence-based polymerase chain reaction. *Infect Control Hosp Epidemiol* 2006; **27**: 981-983 [PMID: 16941328 DOI: 10.1086/507286]

16 **Higgins PG**, Janssen K, Fresen MM, Wisplinghoff H, Seifert H. Molecular epidemiology of Acinetobacter baumannii bloodstream isolates obtained in the United States from 1995 to 2004 using rep-PCR and multilocus sequence typing. *J Clin Microbiol* 2012; **50**: 3493-3500 [PMID: 22895032 DOI: 10.1128/JCM.01759-12]

17 **Lin MF**, Liou ML, Tu CC, Yeh HW, Lan CY. Molecular epidemiology of integron-associated antimicrobial gene cassettes in the clinical isolates of Acinetobacter baumannii from northern Taiwan. *Ann Lab Med* 2013; **33**: 242-247 [PMID: 23826559 DOI: 10.3343/alm.2013.33.4.242]

18 **Seifert H**, Dolzani L, Bressan R, van der Reijden T, van Strijen B, Stefanik D, Heersma H, Dijkshoorn L. Standardization and interlaboratory reproducibility assessment of pulsed-field gel electrophoresis-generated fingerprints of Acinetobacter baumannii. *J Clin Microbiol* 2005; **43**: 4328-4335 [PMID: 16145073 DOI: 10.1128/JCM.43.9.4328-4335.2005]

19 **Zarrilli R**, Crispino M, Bagattini M, Barretta E, Di Popolo A, Triassi M, Villari P. Molecular epidemiology of sequential outbreaks of Acinetobacter baumannii in an intensive care unit shows the emergence of carbapenem resistance. *J Clin Microbiol* 2004; **42**: 946-953 [PMID: 15004037 DOI: 10.1128/jcm.42.3.946-953.2004]

20 **Towner KJ**, Levi K, Vlassiadi M. Genetic diversity of carbapenem-resistant isolates of Acinetobacter baumannii in Europe. *Clin Microbiol Infect* 2008; **14**: 161-167 [PMID: 18093236]

21 **Qi C**, Malczynski M, Parker M, Scheetz MH. Characterization of genetic diversity of carbapenem-resistant Acinetobacter baumannii clinical strains collected from 2004 to 2007. *J Clin Microbiol* 2008; **46**: 1106-1109 [PMID: 18216212 DOI: 10.1128/JCM.01877-07]

22 **Bartual SG**, Seifert H, Hippler C, Luzon MA, Wisplinghoff H, Rodríguez-Valera F. Development of a multilocus sequence typing scheme for characterization of clinical isolates of Acinetobacter baumannii. *J Clin Microbiol* 2005; **43**: 4382-4390 [PMID: 16145081 DOI: 10.1128/JCM.43.9.4382-4390.2005]

23 **Jolley KA**, Maiden MC. BIGSdb: Scalable analysis of bacterial genome variation at the population level. *BMC Bioinformatics* 2010; **11**: 595 [PMID: 21143983 DOI: 10.1186/1471-2105-11-595]

24 **Baumann P**. Isolation of Acinetobacter from soil and water. *J Bacteriol* 1968; **96**: 39-42 [PMID: 4874313]

25 **Peleg AY**, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. *Clin Microbiol Rev* 2008; **21**: 538-582 [PMID: 18625687 DOI: 10.1128/CMR.00058-07]

26 **Fournier PE**, Richet H. The epidemiology and control of Acinetobacter baumannii in health care facilities. *Clin Infect Dis* 2006; **42**: 692-699 [PMID: 16447117 DOI: 10.1086/500202]

27 **Falagas ME**, Karveli EA. The changing global epidemiology of Acinetobacter baumannii infections: a development with major public health implications. *Clin Microbiol Infect* 2007; **13**: 117-119 [PMID: 17328722 DOI: 10.1111/j.1469-0691.2006.01596.x]

28 **Dijkshoorn L**, Nemec A, Seifert H. An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. *Nat Rev Microbiol* 2007; **5**: 939-951 [PMID: 18007677 DOI: 10.1038/nrmicro1789]

29 **Maragakis LL**, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis* 2008; **46**: 1254-1263 [PMID: 18444865 DOI: 10.1086/529198]

30 **Rodríguez-Baño J**, Cisneros JM, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, Martínez-Martínez L, Bou G, Pachón J. Clinical features and epidemiology of Acinetobacter baumannii colonization and infection in Spanish hospitals. *Infect Control Hosp Epidemiol* 2004; **25**: 819-824 [PMID: 15518022]

31 **Lin MF**, Yang CM, Lin CH, Huang ML, Tu CC, Liou ML. Clinical features and molecular epidemiology of multidrug-resistant Acinetobacter calcoaceticus-A baumannii complex in a regional teaching hospital in Taiwan. *Am J Infect Control* 2009; **37**: e1-e3 [PMID: 19576662 DOI: 10.1016/j.ajic.2009.03.008]

32 **Falagas ME**, Bliziotis IA, Siempos II. Attributable mortality of Acinetobacter baumannii infections in critically ill patients: a systematic review of matched cohort and case-control studies. *Crit Care* 2006; **10**: R48 [PMID: 16563184]

33 **Simor AE**, Lee M, Vearncombe M, Jones-Paul L, Barry C, Gomez M, Fish JS, Cartotto RC, Palmer R, Louie M. An out-

break due to multiresistant Acinetobacter baumannii in a burn unit: risk factors for acquisition and management. *Infect Control Hosp Epidemiol* 2002; **23**: 261-267 [PMID: 12026151]

34 **Cisneros JM**, Rodríguez-Baño J, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, Martínez-Martínez L, Bou G, Pachón J. Risk-factors for the acquisition of imipenem-resistant Acinetobacter baumannii in Spain: a nationwide study. *Clin Microbiol Infect* 2005; **11**: 874-879 [PMID: 16216101 DOI: 10.1111/j.1469-0691.2005.01256.x]

35 **Lee SO**, Kim NJ, Choi SH, Hyong Kim T, Chung JW, Woo JH, Ryu J, Kim YS. Risk factors for acquisition of imipenem-resistant Acinetobacter baumannii: a case-control study. *Antimicrob Agents Chemother* 2004; **48**: 224-228 [PMID: 14693543 DOI: 10.1128/aac.48.1.224-228.2004]

36 **Ye JJ**, Huang CT, Shie SS, Huang PY, Su LH, Chiu CH, Leu HS, Chiang PC. Multidrug resistant Acinetobacter baumannii: risk factors for appearance of imipenem resistant strains on patients formerly with susceptible strains. *PLoS One* 2010; **5**: e9947 [PMID: 20369056 DOI: 10.1371/journal.pone.0009947]

37 **Chan MC**, Chiu SK, Hsueh PR, Wang NC, Wang CC, Fang CT. Risk factors for healthcare-associated extensively drug-resistant Acinetobacter baumannii infections: a case-control study. *PLoS One* 2014; **9**: e85973 [PMID: 24465819 DOI: 10.1371/journal.pone.0085973]

38 **Falagas ME**, Kopterides P. Risk factors for the isolation of multi-drug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa: a systematic review of the literature. *J Hosp Infect* 2006; **64**: 7-15 [PMID: 16822583 DOI: 10.1016/j.jhin.2006.04.015]

39 **García-Garmendia JL**, Ortiz-Leyba C, Garnacho-Montero J, Jiménez-Jiménez FJ, Pérez-Paredes C, Barrero-Almodóvar AE, Gili-Miner M. Risk factors for Acinetobacter baumannii nosocomial bacteremia in critically ill patients: a cohort study. *Clin Infect Dis* 2001; **33**: 939-946 [PMID: 11528563]

40 **Park SY**, Choo JW, Kwon SH, Yu SN, Lee EJ, Kim TH, Choo EJ, Jeon MH. Risk Factors for Mortality in Patients with Acinetobacter baumannii Bacteremia. *Infect Chemother* 2013; **45**: 325-330 [PMID: 24396634 DOI: 10.3947/ic.2013.45.3.325]

41 **Baraibar J**, Correa H, Mariscal D, Gallego M, Vallés J, Rello J. Risk factors for infection by Acinetobacter baumannii in intubated patients with nosocomial pneumonia. *Chest* 1997; **112**: 1050-1054 [PMID: 9377916]

42 **Huang ST**, Chiang MC, Kuo SC, Lee YT, Chiang TH, Yang SP, Ti-Yin TL, Fung CP. Risk factors and clinical outcomes of patients with carbapenem-resistant Acinetobacter baumannii bacteremia. *J Microbiol Immunol Infect* 2012; **45**: 356-362 [PMID: 22575430 DOI: 10.1016/j.jmii.2011.12.009]

43 **Jung JY**, Park MS, Kim SE, Park BH, Son JY, Kim EY, Lim JE, Lee SK, Lee SH, Lee KJ, Kang YA, Kim SK, Chang J, Kim YS. Risk factors for multi-drug resistant Acinetobacter baumannii bacteremia in patients with colonization in the intensive care unit. *BMC Infect Dis* 2010; **10**: 228 [PMID: 20670453 DOI: 10.1186/1471-2334-10-228]

44 **Ng TM**, Teng CB, Lye DC, Apisarnthanarak A. A multicenter case-case control study for risk factors and outcomes of extensively drug-resistant Acinetobacter baumannii bacteremia. *Infect Control Hosp Epidemiol* 2014; **35**: 49-55 [PMID: 24334798 DOI: 10.1086/674387]

45 **Zheng YL**, Wan YF, Zhou LY, Ye ML, Liu S, Xu CQ, He YQ, Chen JH. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. *Am J Infect Control* 2013; **41**: e59-e63 [PMID: 23523521 DOI: 10.1016/j.ajic.2013.01.006]

46 **Özgür ES**, Horasan ES, Karaca K, Ersöz G, Naycı Atış S, Kaya A. Ventilator-associated pneumonia due to extensive drug-resistant Acinetobacter baumannii: risk factors, clinical features, and outcomes. *Am J Infect Control* 2014; **42**: 206-208 [PMID: 24485378 DOI: 10.1016/j.ajic.2013.09.003]

47 **Antunes LC**, Imperi F, Carattoli A, Visca P. Deciphering the multifactorial nature of Acinetobacter baumannii pathogenicity. *PLoS One* 2011; **6**: e22674 [PMID: 21829642 DOI: 10.1371/journal.pone.0022674]

48 **Gaddy JA**, Actis LA. Regulation of Acinetobacter baumannii biofilm formation. *Future Microbiol* 2009; **4**: 273-278 [PMID: 19327114 DOI: 10.2217/fmb.09.5]

49 **Tomaras AP**, Flagler MJ, Dorsey CW, Gaddy JA, Actis LA. Characterization of a two-component regulatory system from Acinetobacter baumannii that controls biofilm formation and cellular morphology. *Microbiology* 2008; **154**: 3398-3409 [PMID: 18957593 DOI: 10.1099/mic.0.2008/019471-0]

50 **Brossard KA**, Campagnari AA. The Acinetobacter baumannii biofilm-associated protein plays a role in adherence to human epithelial cells. *Infect Immun* 2012; **80**: 228-233 [PMID: 22083703 DOI: 10.1128/IAI.05913-11]

51 **Fattahian Y**, Rasooli I, Mousavi Gargari SL, Rahbar MR, Darvish Alipour Astaneh S, Amani J. Protection against Acinetobacter baumannii infection via its functional deprivation of biofilm associated protein (Bap). *Microb Pathog* 2011; **51**: 402-406 [PMID: 21946278 DOI: 10.1016/j.micpath.2011.09.004]

52 **Rodríguez-Baño J**, Martí S, Soto S, Fernández-Cuenca F, Cisneros JM, Pachón J, Pascual A, Martínez-Martínez L, McQueary C, Actis LA, Vila J. Biofilm formation in Acinetobacter baumannii: associated features and clinical implications. *Clin Microbiol Infect* 2008; **14**: 276-278 [PMID: 18190568 DOI: 10.1111/j.1469-0691.2007.01916.x]

53 **Marti S**, Nait Chabane Y, Alexandre S, Coquet L, Vila J, Jouenne T, Dé E. Growth of Acinetobacter baumannii in pellicle enhanced the expression of potential virulence factors. *PLoS One* 2011; **6**: e26030 [PMID: 22046254 DOI: 10.1371/journal.pone.0026030]

54 **Eijkelkamp BA**, Hassan KA, Paulsen IT, Brown MH. Investigation of the human pathogen Acinetobacter baumannii under iron limiting conditions. *BMC Genomics* 2011; **12**: 126 [PMID: 21342532 DOI: 10.1186/1471-2164-12-126]

55 **Mortensen BL**, Skaar EP. The contribution of nutrient metal acquisition and metabolism to Acinetobacter baumannii survival within the host. *Front Cell Infect Microbiol* 2013; **3**: 95 [PMID: 24377089 DOI: 10.3389/fcimb.2013.00095]

56 **Hood MI**, Mortensen BL, Moore JL, Zhang Y, Kehl-Fie TE, Sugitani N, Chazin WJ, Caprioli RM, Skaar EP. Identification of an Acinetobacter baumannii zinc acquisition system that facilitates resistance to calprotectin-mediated zinc sequestration. *PLoS Pathog* 2012; **8**: e1003068 [PMID: 23236280 DOI: 10.1371/journal.ppat.1003068]

57 **Lee JC**, Koerten H, van den Broek P, Beekhuizen H, Wolterbeek R, van den Barselaar M, van der Reijden T, van der Meer J, van de Gevel J, Dijkshoorn L. Adherence of Acinetobacter baumannii strains to human bronchial epithelial cells. *Res Microbiol* 2006; **157**: 360-366 [PMID: 16326077 DOI: 10.1016/j.resmic.2005.09.011]

58 **Russo TA**, Luke NR, Beanan JM, Olson R, Sauberan SL, MacDonald U, Schultz LW, Umland TC, Campagnari AA. The K1 capsular polysaccharide of Acinetobacter baumannii strain 307-0294 is a major virulence factor. *Infect Immun* 2010; **78**: 3993-4000 [PMID: 20643860 DOI: 10.1128/IAI.00366-10]

59 **Choi CH**, Lee EY, Lee YC, Park TI, Kim HJ, Hyun SH, Kim SA, Lee SK, Lee JC. Outer membrane protein 38 of Acinetobacter baumannii localizes to the mitochondria and induces apoptosis of epithelial cells. *Cell Microbiol* 2005; **7**: 1127-1138 [PMID: 16008580 DOI: 10.1111/j.1462-5822.2005.00538.x]

60 **Aranda J**, Bardina C, Beceiro A, Rumbo S, Cabral MP, Barbé J, Bou G. Acinetobacter baumannii RecA protein in repair of DNA damage, antimicrobial resistance, general stress response, and virulence. *J Bacteriol* 2011; **193**: 3740-3747 [PMID: 21642465 DOI: 10.1128/JB.00389-11]

61 **Jacobs AC**, Hood I, Boyd KL, Olson PD, Morrison JM, Carson S, Sayood K, Iwen PC, Skaar EP, Dunman PM. Inactivation of phospholipase D diminishes Acinetobacter baumannii pathogenesis. *Infect Immun* 2010; **78**: 1952-1962 [PMID:

20194595 DOI: 10.1128/IAI.00889-09]
62 **Choi CH**, Hyun SH, Lee JY, Lee JS, Lee YS, Kim SA, Chae JP, Yoo SM, Lee JC. Acinetobacter baumannii outer membrane protein A targets the nucleus and induces cytotoxicity. *Cell Microbiol* 2008; **10**: 309-319 [PMID: 17760880 DOI: 10.1111/j.1462-5822.2007.01041.x]
63 **Sugawara E**, Nikaido H. OmpA is the principal nonspecific slow porin of Acinetobacter baumannii. *J Bacteriol* 2012; **194**: 4089-4096 [PMID: 22636785 DOI: 10.1128/JB.00435-12]
64 **Moffatt JH**, Harper M, Harrison P, Hale JD, Vinogradov E, Seemann T, Henry R, Crane B, St Michael F, Cox AD, Adler B, Nation RL, Li J, Boyce JD. Colistin resistance in Acinetobacter baumannii is mediated by complete loss of lipopolysaccharide production. *Antimicrob Agents Chemother* 2010; **54**: 4971-4977 [PMID: 20855724 DOI: 10.1128/AAC.00834-10]
65 **Henry R**, Vithanage N, Harrison P, Seemann T, Coutts S, Moffatt JH, Nation RL, Li J, Harper M, Adler B, Boyce JD. Colistin-resistant, lipopolysaccharide-deficient Acinetobacter baumannii responds to lipopolysaccharide loss through increased expression of genes involved in the synthesis and transport of lipoproteins, phospholipids, and poly-β-1,6-N-acetylglucosamine. *Antimicrob Agents Chemother* 2012; **56**: 59-69 [PMID: 22024825 DOI: 10.1128/AAC.05191-11]
66 **Perez F**, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant Acinetobacter baumannii. *Antimicrob Agents Chemother* 2007; **51**: 3471-3484 [PMID: 17646423 DOI: 10.1128/AAC.01464-06]
67 **Morfin-Otero R**, Dowzicky MJ. Changes in MIC within a global collection of Acinetobacter baumannii collected as part of the Tigecycline Evaluation and Surveillance Trial, 2004 to 2009. *Clin Ther* 2012; **34**: 101-112 [PMID: 22177546 DOI: 10.1016/j.clinthera.2011.11.028]
68 **Hsueh PR**, Teng LJ, Chen CY, Chen WH, Yu CJ, Ho SW, Luh KT. Pandrug-resistant Acinetobacter baumannii causing nosocomial infections in a university hospital, Taiwan. *Emerg Infect Dis* 2002; **8**: 827-832 [PMID: 12141969 DOI: 10.3201/eid0805.020014]
69 **Wang SH**, Sheng WH, Chang YY, Wang LH, Lin HC, Chen ML, Pan HJ, Ko WJ, Chang SC, Lin FY. Healthcare-associated outbreak due to pan-drug resistant Acinetobacter baumannii in a surgical intensive care unit. *J Hosp Infect* 2003; **53**: 97-102 [PMID: 12586567]
70 **Chang PY**, Hsueh PR, Wu PS, Chan PC, Yang TT, Lu CY, Chang LY, Chen JM, Lee PI, Lee CY, Huang LM. Multidrug-resistant Acinetobacter baumannii isolates in pediatric patients of a university hospital in Taiwan. *J Microbiol Immunol Infect* 2007; **40**: 406-410 [PMID: 17932600]
71 **Chang HL**, Tang CH, Hsu YM, Wan L, Chang YF, Lin CT, Tseng YR, Lin YJ, Sheu JJ, Lin CW, Chang YC, Ho MW, Lin CD, Ho CM, Lai CH. Nosocomial outbreak of infection with multidrug-resistant Acinetobacter baumannii in a medical center in Taiwan. *Infect Control Hosp Epidemiol* 2009; **30**: 34-38 [PMID: 19049437 DOI: 10.1086/592704]
72 **Lee YT**, Fung CP, Wang FD, Chen CP, Chen TL, Cho WL. Outbreak of imipenem-resistant Acinetobacter calcoaceticus-Acinetobacter baumannii complex harboring different carbapenemase gene-associated genetic structures in an intensive care unit. *J Microbiol Immunol Infect* 2012; **45**: 43-51 [PMID: 22169123 DOI: 10.1016/j.jmii.2011.09.020]
73 **Lauderdale TL**, Clifford McDonald L, Shiau YR, Chen PC, Wang HY, Lai JF, Ho M. The status of antimicrobial resistance in Taiwan among gram-negative pathogens: the Taiwan surveillance of antimicrobial resistance (TSAR) program, 2000. *Diagn Microbiol Infect Dis* 2004; **48**: 211-219 [PMID: 15023432 DOI: 10.1016/j.diagmicrobio.2003.10.005]
74 **Hsueh PR**, Liu YC, Yang D, Yan JJ, Wu TL, Huang WK, Wu JJ, Ko WC, Leu HS, Yu CR, Luh KT. Multicenter surveillance of antimicrobial resistance of major bacterial pathogens in intensive care units in 2000 in Taiwan. *Microb Drug Resist* 2001; **7**: 373-382 [PMID: 11822777]
75 **Kuo SC**, Chang SC, Wang HY, Lai JF, Chen PC, Shiau YR, Huang IW, Lauderdale TL. Emergence of extensively drug-resistant Acinetobacter baumannii complex over 10 years: nationwide data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. *BMC Infect Dis* 2012; **12**: 200 [PMID: 22929085 DOI: 10.1186/1471-2334-12-200]
76 **Su CH**, Wang JT, Hsiung CA, Chien LJ, Chi CL, Yu HT, Chang FY, Chang SC. Increase of carbapenem-resistant Acinetobacter baumannii infection in acute care hospitals in Taiwan: association with hospital antimicrobial usage. *PLoS One* 2012; **7**: e37788 [PMID: 22629456 DOI: 10.1371/journal.pone.0037788]
77 **Lin MF**, Chang KC, Lan CY, Chou J, Kuo JW, Chang CK, Liou ML. Molecular epidemiology and antimicrobial resistance determinants of multidrug-resistant Acinetobacter baumannii in five proximal hospitals in Taiwan. *Jpn J Infect Dis* 2011; **64**: 222-227 [PMID: 21617307]
78 **Jeong SH**, Bae IK, Park KO, An YJ, Sohn SG, Jang SJ, Sung KH, Yang KS, Lee K, Young D, Lee SH. Outbreaks of imipenem-resistant Acinetobacter baumannii producing carbapenemases in Korea. *J Microbiol* 2006; **44**: 423-431 [PMID: 16953178]
79 **Bogaerts P**, Naas T, Wybo I, Bauraing C, Soetens O, Piérard D, Nordmann P, Glupczynski Y. Outbreak of infection by carbapenem-resistant Acinetobacter baumannii producing the carbapenemase OXA-58 in Belgium. *J Clin Microbiol* 2006; **44**: 4189-4192 [PMID: 16957031 DOI: 10.1128/JCM.00796-06]
80 **Zarrilli R**, Casillo R, Di Popolo A, Tripodi MF, Bagattini M, Cuccurullo S, Crivaro V, Ragone E, Mattei A, Galdieri N, Triassi M, Utili R. Molecular epidemiology of a clonal outbreak of multidrug-resistant Acinetobacter baumannii in a university hospital in Italy. *Clin Microbiol Infect* 2007; **13**: 481-489 [PMID: 17430339]
81 **Scott P**, Deye G, Srinivasan A, Murray C, Moran K, Hulten E, Fishbain J, Craft D, Riddell S, Lindler L, Mancuso J, Milstrey E, Bautista CT, Patel J, Ewell A, Hamilton T, Gaddy C, Tenney M, Christopher G, Petersen K, Endy T, Petruccelli B. An outbreak of multidrug-resistant Acinetobacter baumannii-calcoaceticus complex infection in the US military health care system associated with military operations in Iraq. *Clin Infect Dis* 2007; **44**: 1577-1584 [PMID: 17516401 DOI: 10.1086/518170]
82 **Marchaim D**, Navon-Venezia S, Leavitt A, Chmelnitsky I, Schwaber MJ, Carmeli Y. Molecular and epidemiologic study of polyclonal outbreaks of multidrug-resistant Acinetobacter baumannii infection in an Israeli hospital. *Infect Control Hosp Epidemiol* 2007; **28**: 945-950 [PMID: 17620242 DOI: 10.1086/518970]
83 **Markogiannakis A**, Fildisis G, Tsiplakou S, Ikonomidis A, Koutsoukou A, Pournaras S, Manolis EN, Baltopoulos G, Tsakris A. Cross-transmission of multidrug-resistant Acinetobacter baumannii clonal strains causing episodes of sepsis in a trauma intensive care unit. *Infect Control Hosp Epidemiol* 2008; **29**: 410-417 [PMID: 18419362 DOI: 10.1086/533545]
84 **Shelburne SA**, Singh KV, White AC, Byrne L, Carmer A, Austin C, Graviss E, Stager C, Murray BE, Atmar RL. Sequential outbreaks of infections by distinct Acinetobacter baumannii strains in a public teaching hospital in Houston, Texas. *J Clin Microbiol* 2008; **46**: 198-205 [PMID: 18003801 DOI: 10.1128/JCM.01459-07]
85 **Martins AF**, Kuchenbecker RS, Pilger KO, Pagano M, Barth AL. High endemic levels of multidrug-resistant Acinetobacter baumannii among hospitals in southern Brazil. *Am J Infect Control* 2012; **40**: 108-112 [PMID: 21784555 DOI: 10.1016/j.ajic.2011.03.010]
86 **Runnegar N**, Sidjabat H, Goh HM, Nimmo GR, Schembri MA, Paterson DL. Molecular epidemiology of multidrug-resistant Acinetobacter baumannii in a single institution over a 10-year period. *J Clin Microbiol* 2010; **48**: 4051-4056 [PMID: 20739495 DOI: 10.1128/JCM.01208-10]

87 **Yan ZQ**, Shen DX, Cao JR, Chen R, Wei X, Liu LP, Xu XL. Susceptibility patterns and molecular epidemiology of multidrug-resistant Acinetobacter baumannii strains from three military hospitals in China. *Int J Antimicrob Agents* 2010; **35**: 269-273 [PMID: 20036519 DOI: 10.1016/j.ijantimicag.2009.10.016]

88 **Fillaux J**, Dubouix A, Conil JM, Laguerre J, Marty N. Retrospective analysis of multidrug-resistant Acinetobacter baumannii strains isolated during a 4-year period in a university hospital. *Infect Control Hosp Epidemiol* 2006; **27**: 647-653 [PMID: 16807836 DOI: 10.1086/507082]

89 **Wybo I**, Blommaert L, De Beer T, Soetens O, De Regt J, Lacor P, Piérard D, Lauwers S. Outbreak of multidrug-resistant Acinetobacter baumannii in a Belgian university hospital after transfer of patients from Greece. *J Hosp Infect* 2007; **67**: 374-380 [PMID: 18023922 DOI: 10.1016/j.jhin.2007.09.012]

90 **Mendes RE**, Farrell DJ, Sader HS, Jones RN. Comprehensive assessment of tigecycline activity tested against a worldwide collection of Acinetobacter spp. (2005-2009). *Diagn Microbiol Infect Dis* 2010; **68**: 307-311 [PMID: 20955916 DOI: 10.1016/j.diagmicrobio.2010.07.003]

91 **Quale J**, Bratu S, Landman D, Heddurshetti R. Molecular epidemiology and mechanisms of carbapenem resistance in Acinetobacter baumannii endemic in New York City. *Clin Infect Dis* 2003; **37**: 214-220 [PMID: 12856214 DOI: 10.1086/375821]

92 **Wang H**, Guo P, Sun H, Wang H, Yang Q, Chen M, Xu Y, Zhu Y. Molecular epidemiology of clinical isolates of carbapenem-resistant *Acinetobacter* spp. from Chinese hospitals. *Antimicrob Agents Chemother* 2007; **51**: 4022-4028 [PMID: 17846127 DOI: 10.1128/AAC.01259-06]

93 **Afzal-Shah M**, Livermore DM. Worldwide emergence of carbapenem-resistant Acinetobacter spp. *J Antimicrob Chemother* 1998; **41**: 576-577 [PMID: 9630416]

94 **Young LS**, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant Acinetobacter baumannii infection in a surgical intensive care unit. *Infect Control Hosp Epidemiol* 2007; **28**: 1247-1254 [PMID: 17926275 DOI: 10.1086/521660]

95 **Chan PC**, Huang LM, Lin HC, Chang LY, Chen ML, Lu CY, Lee PI, Chen JM, Lee CY, Pan HJ, Wang JT, Chang SC, Chen YC. Control of an outbreak of pandrug-resistant Acinetobacter baumannii colonization and infection in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2007; **28**: 423-429 [PMID: 17385148 DOI: 10.1086/513120]

96 **Fournier PE**, Vallenet D, Barbe V, Audic S, Ogata H, Poirel L, Richet H, Robert C, Mangenot S, Abergel C, Nordmann P, Weissenbach J, Raoult D, Claverie JM. Comparative genomics of multidrug resistance in Acinetobacter baumannii. *PLoS Genet* 2006; **2**: e7 [PMID: 16415984 DOI: 10.1371/journal.pgen.0020007]

97 **Smith MG**, Gianoulis TA, Pukatzki S, Mekalanos JJ, Ornston LN, Gerstein M, Snyder M. New insights into Acinetobacter baumannii pathogenesis revealed by high-density pyrosequencing and transposon mutagenesis. *Genes Dev* 2007; **21**: 601-614 [PMID: 17344419 DOI: 10.1101/gad.1510307]

98 **Iacono M**, Villa L, Fortini D, Bordoni R, Imperi F, Bonnal RJ, Sicheritz-Ponten T, De Bellis G, Visca P, Cassone A, Carattoli A. Whole-genome pyrosequencing of an epidemic multidrug-resistant Acinetobacter baumannii strain belonging to the European clone II group. *Antimicrob Agents Chemother* 2008; **52**: 2616-2625 [PMID: 18411315 DOI: 10.1128/AAC.01643-07]

99 **Krizova L**, Dijkshoorn L, Nemec A. Diversity and evolution of AbaR genomic resistance islands in Acinetobacter baumannii strains of European clone I. *Antimicrob Agents Chemother* 2011; **55**: 3201-3206 [PMID: 21537009 DOI: 10.1128/AAC.00221-11]

100 **Zhou H**, Zhang T, Yu D, Pi B, Yang Q, Zhou J, Hu S, Yu Y. Genomic analysis of the multidrug-resistant Acinetobacter baumannii strain MDR-ZJ06 widely spread in China. *Antimicrob Agents Chemother* 2011; **55**: 4506-4512 [PMID: 21788470 DOI: 10.1128/AAC.01134-10]

101 **Gao F**, Wang Y, Liu YJ, Wu XM, Lv X, Gan YR, Song SD, Huang H. Genome sequence of Acinetobacter baumannii MDR-TJ. *J Bacteriol* 2011; **193**: 2365-2366 [PMID: 21398552 DOI: 10.1128/JB.00226-11]

102 **Chen CC**, Lin YC, Sheng WH, Chen YC, Chang SC, Hsia KC, Liao MH, Li SY. Genome sequence of a dominant, multidrug-resistant Acinetobacter baumannii strain, TCDC-AB0715. *J Bacteriol* 2011; **193**: 2361-2362 [PMID: 21398540 DOI: 10.1128/JB.00244-11]

103 **Liou ML**, Liu CC, Lu CW, Hsieh MF, Chang KC, Kuo HY, Lee CC, Chang CT, Yang CY, Tang CY. Genome sequence of Acinetobacter baumannii TYTH-1. *J Bacteriol* 2012; **194**: 6974 [PMID: 23209228 DOI: 10.1128/JB.01860-12]

104 **Liu CC**, Tang CY, Kuo HY, Lu CW, Chang KC, Liou ML. The origin of Acinetobacter baumannii TYTH-1: a comparative genomics study. *Int J Antimicrob Agents* 2013; **41**: 318-324 [PMID: 23402702 DOI: 10.1016/j.ijantimicag.2012.12.010]

105 **Adams MD**, Goglin K, Molyneaux N, Hujer KM, Lavender H, Jamison JJ, MacDonald IJ, Martin KM, Russo T, Campagnari AA, Hujer AM, Bonomo RA, Gill SR. Comparative genome sequence analysis of multidrug-resistant Acinetobacter baumannii. *J Bacteriol* 2008; **190**: 8053-8064 [PMID: 18931120 DOI: 10.1128/JB.00834-08]

106 **Adams MD**, Chan ER, Molyneaux ND, Bonomo RA. Genomewide analysis of divergence of antibiotic resistance determinants in closely related isolates of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2010; **54**: 3569-3577 [PMID: 20530228 DOI: 10.1128/AAC.00057-10]

107 **Snitkin ES**, Zelazny AM, Montero CI, Stock F, Mijares L, Murray PR, Segre JA. Genome-wide recombination drives diversification of epidemic strains of Acinetobacter baumannii. *Proc Natl Acad Sci USA* 2011; **108**: 13758-13763 [PMID: 21825119 DOI: 10.1073/pnas.1104404108]

108 **Vallenet D**, Nordmann P, Barbe V, Poirel L, Mangenot S, Bataille E, Dossat C, Gas S, Kreimeyer A, Lenoble P, Oztas S, Poulain J, Segurens B, Robert C, Abergel C, Claverie JM, Raoult D, Médigue C, Weissenbach J, Cruveiller S. Comparative analysis of Acinetobacters: three genomes for three lifestyles. *PLoS One* 2008; **3**: e1805 [PMID: 18350144 DOI: 10.1371/journal.pone.0001805]

109 **Gordon NC**, Wareham DW. Multidrug-resistant Acinetobacter baumannii: mechanisms of virulence and resistance. *Int J Antimicrob Agents* 2010; **35**: 219-226 [PMID: 20047818 DOI: 10.1016/j.ijantimicag.2009.10.024]

110 **Esterly J,** Richardson CL, Eltoukhy NS, Qi C, Scheetz MH. Genetic Mechanisms of Antimicrobial Resistance of Acinetobacter baumannii (February). *Ann Pharmacother* 2011 Feb 8; Epub ahead of print [PMID: 21304033 DOI: 10.1345/aph.1P084]

111 **Roca I**, Espinal P, Vila-Farrés X, Vila J. The Acinetobacter baumannii Oxymoron: Commensal Hospital Dweller Turned Pan-Drug-Resistant Menace. *Front Microbiol* 2012; **3**: 148 [PMID: 22536199 DOI: 10.3389/fmicb.2012.00148]

112 **Kim YJ**, Kim SI, Kim YR, Hong KW, Wie SH, Park YJ, Jeong H, Kang MW. Carbapenem-resistant Acinetobacter baumannii: diversity of resistant mechanisms and risk factors for infection. *Epidemiol Infect* 2012; **140**: 137-145 [PMID: 21554783 DOI: 10.1017/S0950268811000744]

113 **Poirel L**, Nordmann P. Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology. *Clin Microbiol Infect* 2006; **12**: 826-836 [PMID: 16882287 DOI: 10.1111/j.1469-0691.2006.01456.x]

114 **Turton JF**, Ward ME, Woodford N, Kaufmann ME, Pike R, Livermore DM, Pitt TL. The role of ISAba1 in expression of OXA carbapenemase genes in Acinetobacter baumannii. *FEMS Microbiol Lett* 2006; **258**: 72-77 [PMID: 16630258 DOI: 10.1111/j.1574-6968.2006.00195.x]

115 **Bogaerts P**, Naas T, El Garch F, Cuzon G, Deplano A, Delaire

T, Huang TD, Lissoir B, Nordmann P, Glupczynski Y. GES extended-spectrum β-lactamases in Acinetobacter baumannii isolates in Belgium. *Antimicrob Agents Chemother* 2010; **54**: 4872-4878 [PMID: 20805394 DOI: 10.1128/AAC.00871-10]

116 **Chen TL**, Wu RC, Shaio MF, Fung CP, Cho WL. Acquisition of a plasmid-borne blaOXA-58 gene with an upstream IS1008 insertion conferring a high level of carbapenem resistance to Acinetobacter baumannii. *Antimicrob Agents Chemother* 2008; **52**: 2573-2580 [PMID: 18443121 DOI: 10.1128/AAC.00393-08]

117 **Mugnier PD**, Poirel L, Nordmann P. Functional analysis of insertion sequence ISAba1, responsible for genomic plasticity of Acinetobacter baumannii. *J Bacteriol* 2009; **191**: 2414-2418 [PMID: 19136598 DOI: 10.1128/JB.01258-08]

118 **Ravasi P**, Limansky AS, Rodriguez RE, Viale AM, Mussi MA. ISAba825, a functional insertion sequence modulating genomic plasticity and bla(OXA-58) expression in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2011; **55**: 917-920 [PMID: 21098239 DOI: 10.1128/AAC.00491-10]

119 **Chen CH**, Young TG, Huang CC. Predictive biomarkers for drug-resistant Acinetobacter baumannii isolates with bla(TEM-1), AmpC-type bla and integrase 1 genotypes. *J Microbiol Immunol Infect* 2006; **39**: 372-379 [PMID: 17066198]

120 **Endimiani A**, Luzzaro F, Migliavacca R, Mantengoli E, Hujer AM, Hujer KM, Pagani L, Bonomo RA, Rossolini GM, Toniolo A. Spread in an Italian hospital of a clonal Acinetobacter baumannii strain producing the TEM-92 extended-spectrum beta-lactamase. *Antimicrob Agents Chemother* 2007; **51**: 2211-2214 [PMID: 17404005 DOI: 10.1128/AAC.01139-06]

121 **Krizova L**, Poirel L, Nordmann P, Nemec A. TEM-1 β-lactamase as a source of resistance to sulbactam in clinical strains of Acinetobacter baumannii. *J Antimicrob Chemother* 2013; **68**: 2786-2791 [PMID: 23838947 DOI: 10.1093/jac/dkt275]

122 **Naas T**, Namdari F, Réglier-Poupet H, Poyart C, Nordmann P. Panresistant extended-spectrum beta-lactamase SHV-5-producing Acinetobacter baumannii from New York City. *J Antimicrob Chemother* 2007; **60**: 1174-1176 [PMID: 17881631 DOI: 10.1093/jac/dkm366]

123 **Nagano N**, Nagano Y, Cordevant C, Shibata N, Arakawa Y. Nosocomial transmission of CTX-M-2 beta-lactamase-producing Acinetobacter baumannii in a neurosurgery ward. *J Clin Microbiol* 2004; **42**: 3978-3984 [PMID: 15364979 DOI: 10.1128/JCM.42.9.3978-3984.2004]

124 **Potron A**, Munoz-Price LS, Nordmann P, Cleary T, Poirel L. Genetic features of CTX-M-15-producing Acinetobacter baumannii from Haiti. *Antimicrob Agents Chemother* 2011; **55**: 5946-5948 [PMID: 21930877 DOI: 10.1128/AAC.05124-11]

125 **Moubareck C**, Brémont S, Conroy MC, Courvalin P, Lambert T. GES-11, a novel integron-associated GES variant in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2009; **53**: 3579-3581 [PMID: 19451292 DOI: 10.1128/AAC.00072-09]

126 **Poirel L**, Corvec S, Rapoport M, Mugnier P, Petroni A, Pasteran F, Faccone D, Galas M, Drugeon H, Cattoir V, Nordmann P. Identification of the novel narrow-spectrum beta-lactamase SCO-1 in Acinetobacter spp. from Argentina. *Antimicrob Agents Chemother* 2007; **51**: 2179-2184 [PMID: 17420213 DOI: 10.1128/AAC.01600-06]

127 **Jeong SH**, Bae IK, Kwon SB, Lee K, Yong D, Woo GJ, Lee JH, Jung HI, Jang SJ, Sung KH, Lee SH. Investigation of a nosocomial outbreak of Acinetobacter baumannii producing PER-1 extended-spectrum beta-lactamase in an intensive care unit. *J Hosp Infect* 2005; **59**: 242-248 [PMID: 15694982 DOI: 10.1016/j.jhin.2004.09.025]

128 **Poirel L**, Cabanne L, Vahaboglu H, Nordmann P. Genetic environment and expression of the extended-spectrum beta-lactamase blaPER-1 gene in gram-negative bacteria. *Antimicrob Agents Chemother* 2005; **49**: 1708-1713 [PMID: 15855485 DOI: 10.1128/AAC.49.5.1708-1713.2005]

129 **Bonnin RA**, Potron A, Poirel L, Lecuyer H, Neri R, Nordmann P. PER-7, an extended-spectrum beta-lactamase with increased activity toward broad-spectrum cephalosporins in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2011; **55**: 2424-2427 [PMID: 21383087 DOI: 10.1128/AAC.01795-10]

130 **Opazo A**, Sonnevend A, Lopes B, Hamouda A, Ghazawi A, Pal T, Amyes SG. Plasmid-encoded PER-7 β-lactamase responsible for ceftazidime resistance in Acinetobacter baumannii isolated in the United Arab Emirates. *J Antimicrob Chemother* 2012; **67**: 1619-1622 [PMID: 22419799 DOI: 10.1093/jac/dks087]

131 **Naas T**, Coignard B, Carbonne A, Blanckaert K, Bajolet O, Bernet C, Verdeil X, Astagneau P, Desenclos JC, Nordmann P. VEB-1 Extended-spectrum beta-lactamase-producing Acinetobacter baumannii, France. *Emerg Infect Dis* 2006; **12**: 1214-1222 [PMID: 16965700]

132 **Pasterán F**, Rapoport M, Petroni A, Faccone D, Corso A, Galas M, Vázquez M, Procopio A, Tokumoto M, Cagnoni V. Emergence of PER-2 and VEB-1a in Acinetobacter baumannii Strains in the Americas. *Antimicrob Agents Chemother* 2006; **50**: 3222-3224 [PMID: 16940137 DOI: 10.1128/AAC.00284-06]

133 **Poirel L**, Mugnier PD, Toleman MA, Walsh TR, Rapoport MJ, Petroni A, Nordmann P. ISCR2, another vehicle for bla(VEB) gene acquisition. *Antimicrob Agents Chemother* 2009; **53**: 4940-4943 [PMID: 19704129 DOI: 10.1128/AAC.00414-09]

134 **Potron A**, Poirel L, Croizé J, Chanteperdrix V, Nordmann P. Genetic and biochemical characterization of the first extended-spectrum CARB-type beta-lactamase, RTG-4, from Acinetobacter baumannii. *Antimicrob Agents Chemother* 2009; **53**: 3010-3016 [PMID: 19380596 DOI: 10.1128/AAC.01164-08]

135 **Ramírez MS**, Piñeiro S, Centrón D. Novel insights about class 2 integrons from experimental and genomic epidemiology. *Antimicrob Agents Chemother* 2010; **54**: 699-706 [PMID: 19917745 DOI: 10.1128/AAC.01392-08]

136 **Robledo IE**, Aquino EE, Santé MI, Santana JL, Otero DM, León CF, Vázquez GJ. Detection of KPC in Acinetobacter spp. in Puerto Rico. *Antimicrob Agents Chemother* 2010; **54**: 1354-1357 [PMID: 20038618 DOI: 10.1128/AAC.00899-09]

137 **Vahaboglu H**, Oztürk R, Aygün G, Coşkunkan F, Yaman A, Kaygusuz A, Leblebicioglu H, Balik I, Aydin K, Otkun M. Widespread detection of PER-1-type extended-spectrum beta-lactamases among nosocomial Acinetobacter and Pseudomonas aeruginosa isolates in Turkey: a nationwide multicenter study. *Antimicrob Agents Chemother* 1997; **41**: 2265-2269 [PMID: 9333059]

138 **Cornaglia G**, Giamarellou H, Rossolini GM. Metallo-β-lactamases: a last frontier for β-lactams? *Lancet Infect Dis* 2011; **11**: 381-393 [PMID: 21530894 DOI: 10.1016/s1473-3099(11)70056-1]

139 **Yum JH**, Yi K, Lee H, Yong D, Lee K, Kim JM, Rossolini GM, Chong Y. Molecular characterization of metallo-beta-lactamase-producing Acinetobacter baumannii and Acinetobacter genomospecies 3 from Korea: identification of two new integrons carrying the bla(VIM-2) gene cassettes. *J Antimicrob Chemother* 2002; **49**: 837-840 [PMID: 12003980 DOI: 10.1093/jac/dkf043]

140 **Tsakris A**, Ikonomidis A, Pournaras S, Tzouvelekis LS, Sofianou D, Legakis NJ, Maniatis AN. VIM-1 metallo-beta-lactamase in Acinetobacter baumannii. *Emerg Infect Dis* 2006; **12**: 981-983 [PMID: 16707056]

141 **Tsakris A**, Ikonomidis A, Poulou A, Spanakis N, Vrizas D, Diomidous M, Pournaras S, Markou F. Clusters of imipenem-resistant Acinetobacter baumannii clones producing different carbapenemases in an intensive care unit. *Clin Microbiol Infect* 2008; **14**: 588-594 [PMID: 18397334 DOI: 10.1111/j.1469-0691.2008.01996.x]

142 **Papa A**, Koulourida V, Souliou E. Molecular epidemiology of carbapenem-resistant Acinetobacter baumannii in a newly established Greek hospital. *Microb Drug Resist* 2009; **15**: 257-260 [PMID: 19857131 DOI: 10.1089/mdr.2009.0060]

143 **Lee MF**, Peng CF, Hsu HJ, Chen YH. Molecular characterisation of the metallo-beta-lactamase genes in imipenem-resistant Gram-negative bacteria from a university hospital in southern Taiwan. *Int J Antimicrob Agents* 2008; **32**: 475-480

[PMID: 18804966 DOI: 10.1016/j.ijantimicag.2008.07.009]
144 **Tognim MC**, Gales AC, Penteado AP, Silbert S, Sader HS. Dissemination of IMP-1 metallo- beta -lactamase-producing Acinetobacter species in a Brazilian teaching hospital. *Infect Control Hosp Epidemiol* 2006; **27**: 742-747 [PMID: 16807851]
145 **Riccio ML**, Franceschini N, Boschi L, Caravelli B, Cornaglia G, Fontana R, Amicosante G, Rossolini GM. Characterization of the metallo-beta-lactamase determinant of Acinetobacter baumannii AC-54/97 reveals the existence of bla(IMP) allelic variants carried by gene cassettes of different phylogeny. *Antimicrob Agents Chemother* 2000; **44**: 1229-1235 [PMID: 10770756 DOI: 10.1128/aac.44.5.1229-1235.2000]
146 **Chu YW**, Afzal-Shah M, Houang ET, Palepou MI, Lyon DJ, Woodford N, Livermore DM. IMP-4, a novel metallo-beta-lactamase from nosocomial Acinetobacter spp. collected in Hong Kong between 1994 and 1998. *Antimicrob Agents Chemother* 2001; **45**: 710-714 [PMID: 11181348 DOI: 10.1128/AAC.45.3.710-714.2001]
147 **Koh TH**, Sng LH, Wang GC, Hsu LY, Zhao Y. IMP-4 and OXA beta-lactamases in Acinetobacter baumannii from Singapore. *J Antimicrob Chemother* 2007; **59**: 627-632 [PMID: 17284537 DOI: 10.1093/jac/dkl544]
148 **Da Silva GJ**, Correia M, Vital C, Ribeiro G, Sousa JC, Leitão R, Peixe L, Duarte A. Molecular characterization of bla(IMP-5), a new integron-borne metallo-beta-lactamase gene from an Acinetobacter baumannii nosocomial isolate in Portugal. *FEMS Microbiol Lett* 2002; **215**: 33-39 [PMID: 12393197]
149 **Gales AC**, Tognim MC, Reis AO, Jones RN, Sader HS. Emergence of an IMP-like metallo-enzyme in an Acinetobacter baumannii clinical strain from a Brazilian teaching hospital. *Diagn Microbiol Infect Dis* 2003; **45**: 77-79 [PMID: 12573555 DOI: 10.1016/S0732-8893(02)00500-X]
150 **Yamamoto M**, Nagao M, Matsumura Y, Matsushima A, Ito Y, Takakura S, Ichiyama S. Interspecies dissemination of a novel class 1 integron carrying blaIMP-19 among Acinetobacter species in Japan. *J Antimicrob Chemother* 2011; **66**: 2480-2483 [PMID: 21862476 DOI: 10.1093/jac/dkr336]
151 **Lee K**, Yum JH, Yong D, Lee HM, Kim HD, Docquier JD, Rossolini GM, Chong Y. Novel acquired metallo-beta-lactamase gene, bla(SIM-1), in a class 1 integron from Acinetobacter baumannii clinical isolates from Korea. *Antimicrob Agents Chemother* 2005; **49**: 4485-4491 [PMID: 16251286 DOI: 10.1128/AAC.49.11.4485-4491.2005]
152 **Chen Y**, Zhou Z, Jiang Y, Yu Y. Emergence of NDM-1-producing Acinetobacter baumannii in China. *J Antimicrob Chemother* 2011; **66**: 1255-1259 [PMID: 21398294 DOI: 10.1093/jac/dkr082]
153 **Pfeifer Y**, Wilharm G, Zander E, Wichelhaus TA, Göttig S, Hunfeld KP, Seifert H, Witte W, Higgins PG. Molecular characterization of blaNDM-1 in an Acinetobacter baumannii strain isolated in Germany in 2007. *J Antimicrob Chemother* 2011; **66**: 1998-2001 [PMID: 21693460 DOI: 10.1093/jac/dkr256]
154 **Bonnin RA**, Poirel L, Naas T, Pirs M, Seme K, Schrenzel J, Nordmann P. Dissemination of New Delhi metallo-β-lactamase-1-producing Acinetobacter baumannii in Europe. *Clin Microbiol Infect* 2012; **18**: E362-E365 [PMID: 22738206 DOI: 10.1111/j.1469-0691.2012.03928.x]
155 **Espinal P**, Fugazza G, López Y, Kasma M, Lerman Y, Malhotra-Kumar S, Goossens H, Carmeli Y, Vila J. Dissemination of an NDM-2-producing Acinetobacter baumannii clone in an Israeli rehabilitation center. *Antimicrob Agents Chemother* 2011; **55**: 5396-5398 [PMID: 21825296 DOI: 10.1128/AAC.00679-11]
156 **Bou G**, Martínez-Beltrán J. Cloning, nucleotide sequencing, and analysis of the gene encoding an AmpC beta-lactamase in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2000; **44**: 428-432 [PMID: 10639377]
157 **Héritier C**, Poirel L, Nordmann P. Cephalosporinase overexpression resulting from insertion of ISAba1 in Acinetobacter baumannii. *Clin Microbiol Infect* 2006; **12**: 123-130 [PMID: 16441449 DOI: 10.1111/j.1469-0691.2005.01320.x]
158 **Hujer KM**, Hamza NS, Hujer AM, Perez F, Helfand MS, Bethel CR, Thomson JM, Anderson VE, Barlow M, Rice LB, Tenover FC, Bonomo RA. Identification of a new allelic variant of the Acinetobacter baumannii cephalosporinase, ADC-7 beta-lactamase: defining a unique family of class C enzymes. *Antimicrob Agents Chemother* 2005; **49**: 2941-2948 [PMID: 15980372 DOI: 10.1128/AAC.49.7.2941-2948.2005]
159 **Segal H**, Nelson EC, Elisha BG. Genetic environment and transcription of ampC in an Acinetobacter baumannii clinical isolate. *Antimicrob Agents Chemother* 2004; **48**: 612-614 [PMID: 14742218 DOI: 10.1128/aac.48.2.612-614.2004]
160 **Corvec S**, Caroff N, Espaze E, Giraudeau C, Drugeon H, Reynaud A. AmpC cephalosporinase hyperproduction in Acinetobacter baumannii clinical strains. *J Antimicrob Chemother* 2003; **52**: 629-635 [PMID: 12951337 DOI: 10.1093/jac/dkg407]
161 **Bush K**, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. *Antimicrob Agents Chemother* 1995; **39**: 1211-1233 [PMID: 7574506 DOI: 10.1128/aac.39.6.1211]
162 **Walther-Rasmussen J**, Høiby N. OXA-type carbapenemases. *J Antimicrob Chemother* 2006; **57**: 373-383 [PMID: 16446375 DOI: 10.1093/jac/dki482]
163 **Vila J**, Navia M, Ruiz J, Casals C. Cloning and nucleotide sequence analysis of a gene encoding an OXA-derived beta-lactamase in Acinetobacter baumannii. *Antimicrob Agents Chemother* 1997; **41**: 2757-2759 [PMID: 9420053]
164 **Navia MM**, Ruiz J, Vila J. Characterization of an integron carrying a new class D beta-lactamase (OXA-37) in Acinetobacter baumannii. *Microb Drug Resist* 2002; **8**: 261-265 [PMID: 12523622]
165 **Zarrilli R**, Giannouli M, Tomasone F, Triassi M, Tsakris A. Carbapenem resistance in Acinetobacter baumannii: the molecular epidemic features of an emerging problem in health care facilities. *J Infect Dev Ctries* 2009; **3**: 335-341 [PMID: 19759502]
166 **Poirel L**, Naas T, Nordmann P. Diversity, epidemiology, and genetics of class D beta-lactamases. *Antimicrob Agents Chemother* 2010; **54**: 24-38 [PMID: 19721065 DOI: 10.1128/AAC.01512-08]
167 **Mugnier PD**, Poirel L, Naas T, Nordmann P. Worldwide dissemination of the blaOXA-23 carbapenemase gene of Acinetobacter baumannii. *Emerg Infect Dis* 2010; **16**: 35-40 [PMID: 20031040 DOI: 10.3201/eid1601.090852]
168 **Héritier C**, Poirel L, Lambert T, Nordmann P. Contribution of acquired carbapenem-hydrolyzing oxacillinases to carbapenem resistance in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2005; **49**: 3198-3202 [PMID: 16048925 DOI: 10.1128/AAC.49.8.3198-3202.2005]
169 **Naas T**, Levy M, Hirschauer C, Marchandin H, Nordmann P. Outbreak of carbapenem-resistant Acinetobacter baumannii producing the carbapenemase OXA-23 in a tertiary care hospital of Papeete, French Polynesia. *J Clin Microbiol* 2005; **43**: 4826-4829 [PMID: 16145150 DOI: 10.1128/JCM.43.9.4826-4829.2005]
170 **Corvec S**, Poirel L, Naas T, Drugeon H, Nordmann P. Genetics and expression of the carbapenem-hydrolyzing oxacillinase gene blaOXA-23 in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2007; **51**: 1530-1533 [PMID: 17220422 DOI: 10.1128/AAC.01132-06]
171 **Kohlenberg A**, Brümmer S, Higgins PG, Sohr D, Piening BC, de Grahl C, Halle E, Rüden H, Seifert H. Outbreak of carbapenem-resistant Acinetobacter baumannii carrying the carbapenemase OXA-23 in a German university medical centre. *J Med Microbiol* 2009; **58**: 1499-1507 [PMID: 19589905 DOI: 10.1099/jmm.0.012302-0]

172 **Stoeva T**, Higgins PG, Bojkova K, Seifert H. Clonal spread of carbapenem-resistant OXA-23-positive Acinetobacter baumannii in a Bulgarian university hospital. *Clin Microbiol Infect* 2008; **14**: 723-727 [PMID: 18558947 DOI: 10.1111/j.1469-0691.2008.02018.x]

173 **Bonnin RA**, Poirel L, Licker M, Nordmann P. Genetic diversity of carbapenem-hydrolysing β-lactamases in Acinetobacter baumannii from Romanian hospitals. *Clin Microbiol Infect* 2011; **17**: 1524-1528 [PMID: 21883667 DOI: 10.1111/j.1469-0691.2011.03622.x]

174 **Beenken SW**, Karsenty G, Raycroft L, Lozano G. An intron binding protein is required for transformation ability of p53. *Nucleic Acids Res* 1991; **19**: 4747-4752 [PMID: 1891364 DOI: 10.1128/AAC.00226-07]

175 **Chagas TP**, Carvalho KR, de Oliveira Santos IC, Carvalho-Assef AP, Asensi MD. Characterization of carbapenem-resistant Acinetobacter baumannii in Brazil (2008-2011): countrywide spread of OXA-23-producing clones (CC15 and CC79). *Diagn Microbiol Infect Dis* 2014; **79**: 468-472 [PMID: 24880823 DOI: 10.1016/j.diagmicrobio.2014.03.006]

176 **Valenzuela JK**, Thomas L, Partridge SR, van der Reijden T, Dijkshoorn L, Iredell J. Horizontal gene transfer in a polyclonal outbreak of carbapenem-resistant Acinetobacter baumannii. *J Clin Microbiol* 2007; **45**: 453-460 [PMID: 17108068 DOI: 10.1128/JCM.01971-06]

177 **Kuo HY**, Yang CM, Lin MF, Cheng WL, Tien N, Liou ML. Distribution of blaOXA-carrying imipenem-resistant Acinetobacter spp. in 3 hospitals in Taiwan. *Diagn Microbiol Infect Dis* 2010; **66**: 195-199 [PMID: 19836186 DOI: 10.1016/j.diagmicrobio.2009.09.013]

178 **Lin MF**, Kuo HY, Yeh HW, Yang CM, Sung CH, Tu CC, Huang ML, Liou ML. Emergence and dissemination of blaOXA-23-carrying imipenem-resistant Acinetobacter sp in a regional hospital in Taiwan. *J Microbiol Immunol Infect* 2011; **44**: 39-44 [PMID: 21531351 DOI: 10.1016/j.jmii.2011.01.008]

179 **Li Y**, Guo Q, Wang P, Zhu D, Ye X, Wu S, Wang M. Clonal dissemination of extensively drug-resistant Acinetobacter baumannii producing an OXA-23 β-lactamase at a teaching hospital in Shanghai, China. *J Microbiol Immunol Infect* 2014 May 23; Epub ahead of print [PMID: 24863499 DOI: 10.1016/j.jmii.2014.04.005]

180 **Lee Y**, Kim CK, Lee H, Jeong SH, Yong D, Lee K. A novel insertion sequence, ISAba10, inserted into ISAba1 adjacent to the bla(OXA-23) gene and disrupting the outer membrane protein gene carO in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2011; **55**: 361-363 [PMID: 20937784 DOI: 10.1128/AAC.01672-09]

181 **Koh TH**, Tan TT, Khoo CT, Ng SY, Tan TY, Hsu LY, Ooi EE, Van Der Reijden TJ, Dijkshoorn L. Acinetobacter calcoaceticus-Acinetobacter baumannii complex species in clinical specimens in Singapore. *Epidemiol Infect* 2012; **140**: 535-538 [PMID: 21733253 DOI: 10.1017/S0950268811001129]

182 **Principe L**, Piazza A, Giani T, Bracco S, Caltagirone MS, Arena F, Nucleo E, Tammaro F, Rossolini GM, Pagani L, Luzzaro F. Epidemic diffusion of OXA-23-producing Acinetobacter baumannii isolates in Italy: results of the first cross-sectional countrywide survey. *J Clin Microbiol* 2014; **52**: 3004-3010 [PMID: 24920776 DOI: 10.1128/JCM.00291-14]

183 **Mosqueda N**, Espinal P, Cosgaya C, Viota S, Plasensia V, Alvarez-Lerma F, Montero M, Gómez J, Horcajada JP, Vila J, Roca I. Globally expanding carbapenemase finally appears in Spain: nosocomial outbreak of acinetobacter baumannii producing plasmid-encoded OXA-23 in Barcelona, Spain. *Antimicrob Agents Chemother* 2013; **57**: 5155-5157 [PMID: 23877694 DOI: 10.1128/AAC.01486-13]

184 **Poirel L**, Figueiredo S, Cattoir V, Carattoli A, Nordmann P. Acinetobacter radioresistens as a silent source of carbapenem resistance for Acinetobacter spp. *Antimicrob Agents Chemother* 2008; **52**: 1252-1256 [PMID: 18195058 DOI: 10.1128/AAC.01304-07]

185 **Mendes RE**, Bell JM, Turnidge JD, Castanheira M, Jones RN. Emergence and widespread dissemination of OXA-23, -24/40 and -58 carbapenemases among Acinetobacter spp. in Asia-Pacific nations: report from the SENTRY Surveillance Program. *J Antimicrob Chemother* 2009; **63**: 55-59 [PMID: 18957398 DOI: 10.1093/jac/dkn434]

186 **Héritier C**, Poirel L, Fournier PE, Claverie JM, Raoult D, Nordmann P. Characterization of the naturally occurring oxacillinase of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2005; **49**: 4174-4179 [PMID: 16189095 DOI: 10.1128/AAC.49.10.4174-4179.2005]

187 **Brown S**, Young HK, Amyes SG. Characterisation of OXA-51, a novel class D carbapenemase found in genetically unrelated clinical strains of Acinetobacter baumannii from Argentina. *Clin Microbiol Infect* 2005; **11**: 15-23 [PMID: 15649299]

188 **Ruiz M**, Marti S, Fernandez-Cuenca F, Pascual A, Vila J. High prevalence of carbapenem-hydrolysing oxacillinases in epidemiologically related and unrelated Acinetobacter baumannii clinical isolates in Spain. *Clin Microbiol Infect* 2007; **13**: 1192-1198 [PMID: 17850347]

189 **Chen TL**, Lee YT, Kuo SC, Hsueh PR, Chang FY, Siu LK, Ko WC, Fung CP. Emergence and Distribution of Plasmids Bearing the blaOXA-51-like gene with an upstream ISAba1 in carbapenem-resistant Acinetobacter baumannii isolates in Taiwan. *Antimicrob Agents Chemother* 2010; **54**: 4575-4581 [PMID: 20713680 DOI: 10.1128/AAC.00764-10]

190 **Hu WS**, Yao SM, Fung CP, Hsieh YP, Liu CP, Lin JF. An OXA-66/OXA-51-like carbapenemase and possibly an efflux pump are associated with resistance to imipenem in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2007; **51**: 3844-3852 [PMID: 17724156 DOI: 10.1128/AAC.01512-06]

191 **Brown S**, Amyes SG. The sequences of seven class D beta-lactamases isolated from carbapenem-resistant Acinetobacter baumannii from four continents. *Clin Microbiol Infect* 2005; **11**: 326-329 [PMID: 15760431 DOI: 10.1111/j.1469-0691.2005.01096.x]

192 **Turton JF**, Woodford N, Glover J, Yarde S, Kaufmann ME, Pitt TL. Identification of Acinetobacter baumannii by detection of the blaOXA-51-like carbapenemase gene intrinsic to this species. *J Clin Microbiol* 2006; **44**: 2974-2976 [PMID: 16891520 DOI: 10.1128/JCM.01021-06]

193 **Vahaboglu H**, Budak F, Kasap M, Gacar G, Torol S, Karadenizli A, Kolayli F, Eroglu C. High prevalence of OXA-51-type class D beta-lactamases among ceftazidime-resistant clinical isolates of Acinetobacter spp.: co-existence with OXA-58 in multiple centres. *J Antimicrob Chemother* 2006; **58**: 537-542 [PMID: 16816400 DOI: 10.1093/jac/dkl273]

194 **Evans BA**, Brown S, Hamouda A, Findlay J, Amyes SG. Eleven novel OXA-51-like enzymes from clinical isolates of Acinetobacter baumannii. *Clin Microbiol Infect* 2007; **13**: 1137-1138 [PMID: 17850339 DOI: 10.1111/j.1469-0691.2007.01828.x]

195 **Tsakris A**, Ikonomidis A, Spanakis N, Pournaras S, Bethimouti K. Identification of a novel bla(OXA-51) variant, bla(OXA-92), from a clinical isolate of Acinetobacter baumannii. *Clin Microbiol Infect* 2007; **13**: 348-349 [PMID: 17391399 DOI: 10.1111/j.1469-0691.2006.01598.x]

196 **Higgins PG**, Poirel L, Lehmann M, Nordmann P, Seifert H. OXA-143, a novel carbapenem-hydrolyzing class D beta-lactamase in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2009; **53**: 5035-5038 [PMID: 19770279 DOI: 10.1128/AAC.00856-09]

197 **Bou G**, Oliver A, Martínez-Beltrán J. OXA-24, a novel class D beta-lactamase with carbapenemase activity in an Acinetobacter baumannii clinical strain. *Antimicrob Agents Chemother* 2000; **44**: 1556-1561 [PMID: 10817708]

198 **Afzal-Shah M**, Woodford N, Livermore DM. Characterization of OXA-25, OXA-26, and OXA-27, molecular class D

beta-lactamases associated with carbapenem resistance in clinical isolates of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2001; **45**: 583-588 [PMID: 11158758 DOI: 10.1128/AAC.45.2.583-588.2001]

199 **Brown S**, Amyes S. OXA (beta)-lactamases in Acinetobacter: the story so far. *J Antimicrob Chemother* 2006; **57**: 1-3 [PMID: 16332731 DOI: 10.1093/jac/dki425]

200 **Héritier C**, Poirel L, Aubert D, Nordmann P. Genetic and functional analysis of the chromosome-encoded carbapenem-hydrolyzing oxacillinase OXA-40 of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2003; **47**: 268-273 [PMID: 12499201 DOI: 10.1128/aac.47.1.268-273.2003]

201 **Acosta J**, Merino M, Viedma E, Poza M, Sanz F, Otero JR, Chaves F, Bou G. Multidrug-resistant Acinetobacter baumannii Harboring OXA-24 carbapenemase, Spain. *Emerg Infect Dis* 2011; **17**: 1064-1067 [PMID: 21749771 DOI: 10.3201/eid1706.091866]

202 **Quinteira S**, Grosso F, Ramos H, Peixe L. Molecular epidemiology of imipenem-resistant Acinetobacter haemolyticus and Acinetobacter baumannii isolates carrying plasmid-mediated OXA-40 from a Portuguese hospital. *Antimicrob Agents Chemother* 2007; **51**: 3465-3466 [PMID: 17606684 DOI: 10.1128/AAC.00267-07]

203 **Lolans K**, Rice TW, Munoz-Price LS, Quinn JP. Multicity outbreak of carbapenem-resistant Acinetobacter baumannii isolates producing the carbapenemase OXA-40. *Antimicrob Agents Chemother* 2006; **50**: 2941-2945 [PMID: 16940085 DOI: 10.1128/AAC.00116-06]

204 **Merino M**, Acosta J, Poza M, Sanz F, Beceiro A, Chaves F, Bou G. OXA-24 carbapenemase gene flanked by XerC/XerD-like recombination sites in different plasmids from different Acinetobacter species isolated during a nosocomial outbreak. *Antimicrob Agents Chemother* 2010; **54**: 2724-2727 [PMID: 20385865 DOI: 10.1128/AAC.01674-09]

205 **Lu PL**, Doumith M, Livermore DM, Chen TP, Woodford N. Diversity of carbapenem resistance mechanisms in Acinetobacter baumannii from a Taiwan hospital: spread of plasmid-borne OXA-72 carbapenemase. *J Antimicrob Chemother* 2009; **63**: 641-647 [PMID: 19182237 DOI: 10.1093/jac/dkn553]

206 **Goic-Barisic I**, Towner KJ, Kovacic A, Sisko-Kraljevic K, Tonkic M, Novak A, Punda-Polic V. Outbreak in Croatia caused by a new carbapenem-resistant clone of Acinetobacter baumannii producing OXA-72 carbapenemase. *J Hosp Infect* 2011; **77**: 368-369 [PMID: 21316806 DOI: 10.1016/j.jhin.2010.12.003]

207 **Poirel L**, Marqué S, Héritier C, Segonds C, Chabanon G, Nordmann P. OXA-58, a novel class D {beta}-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2005; **49**: 202-208 [PMID: 15616297 DOI: 10.1128/AAC.49.1.202-208.2005]

208 **Coelho J**, Woodford N, Afzal-Shah M, Livermore D. Occurrence of OXA-58-like carbapenemases in Acinetobacter spp. collected over 10 years in three continents. *Antimicrob Agents Chemother* 2006; **50**: 756-758 [PMID: 16436738 DOI: 10.1128/AAC.50.2.756-758.2006]

209 **Marqué S**, Poirel L, Héritier C, Brisse S, Blasco MD, Filip R, Coman G, Naas T, Nordmann P. Regional occurrence of plasmid-mediated carbapenem-hydrolyzing oxacillinase OXA-58 in Acinetobacter spp. in Europe. *J Clin Microbiol* 2005; **43**: 4885-4888 [PMID: 16145167 DOI: 10.1128/JCM.43.9.4885-4888.2005]

210 **Gogou V**, Pournaras S, Giannouli M, Voulgari E, Piperaki ET, Zarrilli R, Tsakris A. Evolution of multidrug-resistant Acinetobacter baumannii clonal lineages: a 10 year study in Greece (2000-09). *J Antimicrob Chemother* 2011; **66**: 2767-2772 [PMID: 21933784 DOI: 10.1093/jac/dkr390]

211 **Donnarumma F**, Sergi S, Indorato C, Mastromei G, Monnanni R, Nicoletti P, Pecile P, Cecconi D, Mannino R, Bencini S, Fanci R, Bosi A, Casalone E. Molecular characterization of acinetobacter isolates collected in intensive care units of six hospitals in Florence, Italy, during a 3-year surveillance program: a population structure analysis. *J Clin Microbiol* 2010; **48**: 1297-1304 [PMID: 20181903 DOI: 10.1128/JCM.01916-09]

212 **Peleg AY**, Franklin C, Walters LJ, Bell JM, Spelman DW. OXA-58 and IMP-4 carbapenem-hydrolyzing beta-lactamases in an Acinetobacter junii blood culture isolate from Australia. *Antimicrob Agents Chemother* 2006; **50**: 399-400 [PMID: 16377723 DOI: 10.1128/AAC.50.1.399-400.2006]

213 **Castanheira M**, Wanger A, Kruzel M, Deshpande LM, Jones RN. Emergence and clonal dissemination of OXA-24- and OXA-58-producing Acinetobacter baumannii strains in Houston, Texas: report from the SENTRY Antimicrobial Surveillance Program. *J Clin Microbiol* 2008; **46**: 3179-3180 [PMID: 18768660 DOI: 10.1128/JCM.00988-08]

214 **Hujer KM**, Hujer AM, Hulten EA, Bajaksouzian S, Adams JM, Donskey CJ, Ecker DJ, Massire C, Eshoo MW, Sampath R, Thomson JM, Rather PN, Craft DW, Fishbain JT, Ewell AJ, Jacobs MR, Paterson DL, Bonomo RA. Analysis of antibiotic resistance genes in multidrug-resistant Acinetobacter sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother* 2006; **50**: 4114-4123 [PMID: 17000742 DOI: 10.1128/AAC.00778-06]

215 **Fu Y**, Jiang J, Zhou H, Jiang Y, Fu Y, Yu Y, Zhou J. Characterization of a novel plasmid type and various genetic contexts of bla OXA-58 in Acinetobacter spp. from multiple cities in China. *PLoS One* 2014; **9**: e84680 [PMID: 24400107 DOI: 10.1371/journal.pone.0084680]

216 **Bertini A**, Giordano A, Varesi P, Villa L, Mancini C, Carattoli A. First report of the carbapenem-hydrolyzing oxacillinase OXA-58 in Acinetobacter baumannii isolates in Italy. *Antimicrob Agents Chemother* 2006; **50**: 2268-2269 [PMID: 16723603 DOI: 10.1128/AAC.00166-06]

217 **Héritier C**, Dubouix A, Poirel L, Marty N, Nordmann P. A nosocomial outbreak of Acinetobacter baumannii isolates expressing the carbapenem-hydrolysing oxacillinase OXA-58. *J Antimicrob Chemother* 2005; **55**: 115-118 [PMID: 15590718 DOI: 10.1093/jac/dkh500]

218 **Poirel L**, Nordmann P. Genetic structures at the origin of acquisition and expression of the carbapenem-hydrolyzing oxacillinase gene blaOXA-58 in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2006; **50**: 1442-1448 [PMID: 16569863 DOI: 10.1128/AAC.50.4.1442-1448.2006]

219 **Pournaras S**, Markogiannakis A, Ikonomidis A, Kondyli L, Bethimouti K, Maniatis AN, Legakis NJ, Tsakris A. Outbreak of multiple clones of imipenem-resistant Acinetobacter baumannii isolates expressing OXA-58 carbapenemase in an intensive care unit. *J Antimicrob Chemother* 2006; **57**: 557-561 [PMID: 16431857 DOI: 10.1093/jac/dkl004]

220 **Poirel L**, Mansour W, Bouallegue O, Nordmann P. Carbapenem-resistant Acinetobacter baumannii isolates from Tunisia producing the OXA-58-like carbapenem-hydrolyzing oxacillinase OXA-97. *Antimicrob Agents Chemother* 2008; **52**: 1613-1617 [PMID: 18299404 DOI: 10.1128/AAC.00978-07]

221 **Kim CK**, Lee Y, Lee H, Woo GJ, Song W, Kim MN, Lee WG, Jeong SH, Lee K, Chong Y. Prevalence and diversity of carbapenemases among imipenem-nonsusceptible Acinetobacter isolates in Korea: emergence of a novel OXA-182. *Diagn Microbiol Infect Dis* 2010; **68**: 432-438 [PMID: 20884158 DOI: 10.1016/j.diagmicrobio.2010.07.014]

222 **Higgins PG**, Pérez-Llarena FJ, Zander E, Fernández A, Bou G, Seifert H. OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2013; **57**: 2121-2126 [PMID: 23439638 DOI: 10.1128/AAC.02413-12]

223 **Piddock LJ**. Multidrug-resistance efflux pumps - not just for resistance. *Nat Rev Microbiol* 2006; **4**: 629-636 [PMID: 16845433 DOI: 10.1038/nrmicro1464]

224 **Hooper DC**. Efflux pumps and nosocomial antibiotic resistance: a primer for hospital epidemiologists. *Clin Infect Dis* 2005; **40**: 1811-1817 [PMID: 15909271 DOI: 10.1086/430381]

225 **Coyne S**, Courvalin P, Périchon B. Efflux-mediated antibiotic resistance in Acinetobacter spp. *Antimicrob Agents Chemother* 2011; **55**: 947-953 [PMID: 21173183 DOI: 10.1128/AAC.01388-10]

226 **Ruzin A**, Keeney D, Bradford PA. AdeABC multidrug efflux pump is associated with decreased susceptibility to tigecycline in Acinetobacter calcoaceticus-Acinetobacter baumannii complex. *J Antimicrob Chemother* 2007; **59**: 1001-1004 [PMID: 17363424 DOI: 10.1093/jac/dkm058]

227 **Peleg AY**, Adams J, Paterson DL. Tigecycline Efflux as a Mechanism for Nonsusceptibility in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2007; **51**: 2065-2069 [PMID: 17420217 DOI: 10.1128/AAC.01198-06]

228 **Ruzin A**, Immermann FW, Bradford PA. RT-PCR and statistical analyses of adeABC expression in clinical isolates of Acinetobacter calcoaceticus-Acinetobacter baumannii complex. *Microb Drug Resist* 2010; **16**: 87-89 [PMID: 20438348 DOI: 10.1089/mdr.2009.0131]

229 **Pannek S**, Higgins PG, Steinke P, Jonas D, Akova M, Bohnert JA, Seifert H, Kern WV. Multidrug efflux inhibition in Acinetobacter baumannii: comparison between 1-(1-naphthylmethyl)-piperazine and phenyl-arginine-beta-naphthylamide. *J Antimicrob Chemother* 2006; **57**: 970-974 [PMID: 16531429 DOI: 10.1093/jac/dkl081]

230 **Coban AY**, Guney AK, Tanriverdi Cayci Y, Durupinar B. Effect of 1-(1-Naphtylmethyl)-piperazine, an efflux pump inhibitor, on antimicrobial drug susceptibilities of clinical Acinetobacter baumannii isolates. *Curr Microbiol* 2011; **62**: 508-511 [PMID: 20717673 DOI: 10.1007/s00284-010-9736-9]

231 **Cortez-Cordova J**, Kumar A. Activity of the efflux pump inhibitor phenylalanine-arginine β-naphthylamide against the AdeFGH pump of Acinetobacter baumannii. *Int J Antimicrob Agents* 2011; **37**: 420-424 [PMID: 21377839 DOI: 10.1016/j.ijantimicag.2011.01.006]

232 **Deng M**, Zhu MH, Li JJ, Bi S, Sheng ZK, Hu FS, Zhang JJ, Chen W, Xue XW, Sheng JF, Li LJ. Molecular epidemiology and mechanisms of tigecycline resistance in clinical isolates of Acinetobacter baumannii from a Chinese university hospital. *Antimicrob Agents Chemother* 2014; **58**: 297-303 [PMID: 24165187 DOI: 10.1128/AAC.01727-13]

233 **Vila J**, Martí S, Sánchez-Céspedes J. Porins, efflux pumps and multidrug resistance in Acinetobacter baumannii. *J Antimicrob Chemother* 2007; **59**: 1210-1215 [PMID: 17324960 DOI: 10.1093/jac/dkl509]

234 **Wieczorek P**, Sacha P, Hauschild T, Zórawski M, Krawczyk M, Tryniszewska E. Multidrug resistant Acinetobacter baumannii--the role of AdeABC (RND family) efflux pump in resistance to antibiotics. *Folia Histochem Cytobiol* 2008; **46**: 257-267 [PMID: 19056528 DOI: 10.2478/v10042-008-0056-x]

235 **Magnet S**, Courvalin P, Lambert T. Resistance-nodulation-cell division-type efflux pump involved in aminoglycoside resistance in Acinetobacter baumannii strain BM4454. *Antimicrob Agents Chemother* 2001; **45**: 3375-3380 [PMID: 11709311 DOI: 10.1128/AAC.45.12.3375-3380.2001]

236 **Hornsey M**, Ellington MJ, Doumith M, Thomas CP, Gordon NC, Wareham DW, Quinn J, Lolans K, Livermore DM, Woodford N. AdeABC-mediated efflux and tigecycline MICs for epidemic clones of Acinetobacter baumannii. *J Antimicrob Chemother* 2010; **65**: 1589-1593 [PMID: 20554571 DOI: 10.1093/jac/dkq218]

237 **Higgins PG**, Wisplinghoff H, Stefanik D, Seifert H. Selection of topoisomerase mutations and overexpression of adeB mRNA transcripts during an outbreak of Acinetobacter baumannii. *J Antimicrob Chemother* 2004; **54**: 821-823 [PMID: 15355942 DOI: 10.1093/jac/dkh427]

238 **Marchand I**, Damier-Piolle L, Courvalin P, Lambert T. Expression of the RND-type efflux pump AdeABC in Acinetobacter baumannii is regulated by the AdeRS two-component system. *Antimicrob Agents Chemother* 2004; **48**: 3298-3304 [PMID: 15328088 DOI: 10.1128/AAC.48.9.3298-3304.2004]

239 **Sun JR**, Perng CL, Chan MC, Morita Y, Lin JC, Su CM, Wang WY, Chang TY, Chiueh TS. A truncated AdeS kinase protein generated by ISAba1 insertion correlates with tigecycline resistance in Acinetobacter baumannii. *PLoS One* 2012; **7**: e49534 [PMID: 23166700 DOI: 10.1371/journal.pone.0049534]

240 **Sun JR**, Chan MC, Chang TY, Wang WY, Chiueh TS. Overexpression of the adeB gene in clinical isolates of tigecycline-nonsusceptible Acinetobacter baumannii without insertion mutations in adeRS. *Antimicrob Agents Chemother* 2010; **54**: 4934-4938 [PMID: 20696871 DOI: 10.1128/AAC.00414-10]

241 **Fernando D**, Kumar A. Growth phase-dependent expression of RND efflux pump- and outer membrane porin-encoding genes in Acinetobacter baumannii ATCC 19606. *J Antimicrob Chemother* 2012; **67**: 569-572 [PMID: 22146875 DOI: 10.1093/jac/dkr519]

242 **Lin MF**, Lin YY, Yeh HW, Lan CY. Role of the BaeSR two-component system in the regulation of Acinetobacter baumannii adeAB genes and its correlation with tigecycline susceptibility. *BMC Microbiol* 2014; **14**: 119 [PMID: 24885279 DOI: 10.1186/1471-2180-14-119]

243 **Coyne S**, Rosenfeld N, Lambert T, Courvalin P, Périchon B. Overexpression of resistance-nodulation-cell division pump AdeFGH confers multidrug resistance in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2010; **54**: 4389-4393 [PMID: 20696879 DOI: 10.1128/AAC.00155-10]

244 **Damier-Piolle L**, Magnet S, Brémont S, Lambert T, Courvalin P. AdeIJK, a resistance-nodulation-cell division pump effluxing multiple antibiotics in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2008; **52**: 557-562 [PMID: 18086852 DOI: 10.1128/AAC.00732-07]

245 **Hou PF**, Chen XY, Yan GF, Wang YP, Ying CM. Study of the correlation of imipenem resistance with efflux pumps AdeABC, AdeIJK, AdeDE and AbeM in clinical isolates of Acinetobacter baumannii. *Chemotherapy* 2012; **58**: 152-158 [PMID: 22614896 DOI: 10.1159/000335599]

246 **Rosenfeld N**, Bouchier C, Courvalin P, Périchon B. Expression of the resistance-nodulation-cell division pump AdeIJK in Acinetobacter baumannii is regulated by AdeN, a TetR-type regulator. *Antimicrob Agents Chemother* 2012; **56**: 2504-2510 [PMID: 22371895 DOI: 10.1128/AAC.06422-11]

247 **Chau SL**, Chu YW, Houang ET. Novel resistance-nodulation-cell division efflux system AdeDE in Acinetobacter genomic DNA group 3. *Antimicrob Agents Chemother* 2004; **48**: 4054-4055 [PMID: 15388479 DOI: 10.1128/AAC.48.10.4054-4055.2004]

248 **Ribera A**, Roca I, Ruiz J, Gibert I, Vila J. Partial characterization of a transposon containing the tet(A) determinant in a clinical isolate of Acinetobacter baumannii. *J Antimicrob Chemother* 2003; **52**: 477-480 [PMID: 12888597 DOI: 10.1093/jac/dkg344]

249 **Roca I**, Marti S, Espinal P, Martínez P, Gibert I, Vila J. CraA, a major facilitator superfamily efflux pump associated with chloramphenicol resistance in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2009; **53**: 4013-4014 [PMID: 19581458 DOI: 10.1128/AAC.00584-09]

250 **Rajamohan G**, Srinivasan VB, Gebreyes WA. Molecular and functional characterization of a novel efflux pump, AmvA, mediating antimicrobial and disinfectant resistance in Acinetobacter baumannii. *J Antimicrob Chemother* 2010; **65**: 1919-1925 [PMID: 20573661 DOI: 10.1093/jac/dkq195]

251 **Su XZ**, Chen J, Mizushima T, Kuroda T, Tsuchiya T. AbeM, an H+-coupled Acinetobacter baumannii multidrug efflux pump belonging to the MATE family of transporters. *Antimicrob Agents Chemother* 2005; **49**: 4362-4364 [PMID: 16189122 DOI: 10.1128/AAC.49.10.4362-4364.2005]

252 **Srinivasan VB**, Rajamohan G, Gebreyes WA. Role of AbeS, a novel efflux pump of the SMR family of transporters, in resistance to antimicrobial agents in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2009; **53**: 5312-5316 [PMID: 19770280 DOI: 10.1128/AAC.00748-09]

253 **Cho YJ**, Moon DC, Jin JS, Choi CH, Lee YC, Lee JC. Genetic basis of resistance to aminoglycosides in Acinetobacter spp. and spread of armA in Acinetobacter baumannii sequence group 1 in Korean hospitals. *Diagn Microbiol Infect Dis* 2009; **64**: 185-190 [PMID: 19361944 DOI: 10.1016/j.diagmicrobio.2009.02.010]

254 **Ramirez MS**, Tolmasky ME. Aminoglycoside modifying enzymes. *Drug Resist Updat* 2010; **13**: 151-171 [PMID: 20833577 DOI: 10.1016/j.drup.2010.08.003]

255 **Gallego L**, Towner KJ. Carriage of class 1 integrons and antibiotic resistance in clinical isolates of Acinetobacter baumannii from northern Spain. *J Med Microbiol* 2001; **50**: 71-77 [PMID: 11192508]

256 **Nemec A**, Dolzani L, Brisse S, van den Broek P, Dijkshoorn L. Diversity of aminoglycoside-resistance genes and their association with class 1 integrons among strains of pan-European Acinetobacter baumannii clones. *J Med Microbiol* 2004; **53**: 1233-1240 [PMID: 15585503 DOI: 10.1099/jmm.0.45716-0]

257 **Zhu J**, Wang C, Wu J, Jiang R, Mi Z, Huang Z. A novel aminoglycoside-modifying enzyme gene aac(6′)-Ib in a pandrug-resistant Acinetobacter baumannii strain. *J Hosp Infect* 2009; **73**: 184-185 [PMID: 19703723 DOI: 10.1016/j.jhin.2009.06.026]

258 **Bakour S**, Alsharapy SA, Touati A, Rolain JM. Characterization of Acinetobacter baumannii Clinical Isolates Carrying blaOXA-23 Carbapenemase and 16S rRNA Methylase armA genes in Yemen. *Microb Drug Resist* 2014 Jun 5; Epub ahead of print [PMID: 24901296 DOI: 10.1089/mdr.2014.0018]

259 **Doi Y**, Wachino J, Yamane K, Shibata N, Yagi T, Shibayama K, Kato H, Arakawa Y. Spread of novel aminoglycoside resistance gene aac(6′)-Iad among Acinetobacter clinical isolates in Japan. *Antimicrob Agents Chemother* 2004; **48**: 2075-2080 [PMID: 15155202 DOI: 10.1128/AAC.48.6.2075-2080.2004]

260 **Ploy MC**, Giamarellou H, Bourlioux P, Courvalin P, Lambert T. Detection of aac(6′)-I genes in amikacin-resistant Acinetobacter spp. by PCR. *Antimicrob Agents Chemother* 1994; **38**: 2925-2928 [PMID: 7695286 DOI: 10.1128/aac.38.12.2925]

261 **Lin MF**, Chang KC, Yang CY, Yang CM, Xiao CC, Kuo HY, Liou ML. Role of integrons in antimicrobial susceptibility patterns of Acinetobacter baumannii. *Jpn J Infect Dis* 2010; **63**: 440-443 [PMID: 21099097]

262 **Gaddy JA**, Tomaras AP, Actis LA. The Acinetobacter baumannii 19606 OmpA protein plays a role in biofilm formation on abiotic surfaces and in the interaction of this pathogen with eukaryotic cells. *Infect Immun* 2009; **77**: 3150-3160 [PMID: 19470746 DOI: 10.1128/IAI.00096-09]

263 **Jin JS**, Kwon SO, Moon DC, Gurung M, Lee JH, Kim SI, Lee JC. Acinetobacter baumannii secretes cytotoxic outer membrane protein A via outer membrane vesicles. *PLoS One* 2011; **6**: e17027 [PMID: 21386968 DOI: 10.1371/journal.pone.0017027]

264 **Siroy A**, Molle V, Lemaître-Guillier C, Vallenet D, Pestel-Caron M, Cozzone AJ, Jouenne T, Dé E. Channel formation by CarO, the carbapenem resistance-associated outer membrane protein of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2005; **49**: 4876-4883 [PMID: 16304148 DOI: 10.1128/AAC.49.12.4876-4883.2005]

265 **Mussi MA**, Limansky AS, Viale AM. Acquisition of resistance to carbapenems in multidrug-resistant clinical strains of Acinetobacter baumannii: natural insertional inactivation of a gene encoding a member of a novel family of beta-barrel outer membrane proteins. *Antimicrob Agents Chemother* 2005; **49**: 1432-1440 [PMID: 15793123 DOI: 10.1128/AAC.49.4.1432-1440.2005]

266 **Mussi MA**, Relling VM, Limansky AS, Viale AM. CarO, an Acinetobacter baumannii outer membrane protein involved in carbapenem resistance, is essential for L-ornithine uptake. *FEBS Lett* 2007; **581**: 5573-5578 [PMID: 17997983 DOI: 10.1016/j.febslet.2007.10.063]

267 **Catel-Ferreira M**, Coadou G, Molle V, Mugnier P, Nordmann P, Siroy A, Jouenne T, Dé E. Structure-function relationships of CarO, the carbapenem resistance-associated outer membrane protein of Acinetobacter baumannii. *J Antimicrob Chemother* 2011; **66**: 2053-2056 [PMID: 21705362 DOI: 10.1093/jac/dkr267]

268 **Bou G**, Cerveró G, Domínguez MA, Quereda C, Martínez-Beltrán J. Characterization of a nosocomial outbreak caused by a multiresistant Acinetobacter baumannii strain with a carbapenem-hydrolyzing enzyme: high-level carbapenem resistance in A. baumannii is not due solely to the presence of beta-lactamases. *J Clin Microbiol* 2000; **38**: 3299-3305 [PMID: 10970374]

269 **del Mar Tomás M**, Beceiro A, Pérez A, Velasco D, Moure R, Villanueva R, Martínez-Beltrán J, Bou G. Cloning and functional analysis of the gene encoding the 33- to 36-kilodalton outer membrane protein associated with carbapenem resistance in Acinetobacter baumannii. *Antimicrob Agents Chemother* 2005; **49**: 5172-5175 [PMID: 16304197 DOI: 10.1128/AAC.49.12.5172-5175.2005]

270 **Hood MI**, Jacobs AC, Sayood K, Dunman PM, Skaar EP. Acinetobacter baumannii increases tolerance to antibiotics in response to monovalent cations. *Antimicrob Agents Chemother* 2010; **54**: 1029-1041 [PMID: 20028819 DOI: 10.1128/AAC.00963-09]

271 **Dupont M**, Pagès JM, Lafitte D, Siroy A, Bollet C. Identification of an OprD homologue in Acinetobacter baumannii. *J Proteome Res* 2005; **4**: 2386-2390 [PMID: 16335991]

272 **Jeong HW**, Cheong HJ, Kim WJ, Kim MJ, Song KJ, Song JW, Kim HS, Roh KH. Loss of the 29-kilodalton outer membrane protein in the presence of OXA-51-like enzymes in Acinetobacter baumannii is associated with decreased imipenem susceptibility. *Microb Drug Resist* 2009; **15**: 151-158 [PMID: 19728771 DOI: 10.1089/mdr.2009.0828]

273 **Fonseca EL**, Scheidegger E, Freitas FS, Cipriano R, Vicente AC. Carbapenem-resistant Acinetobacter baumannii from Brazil: role of carO alleles expression and blaOXA-23 gene. *BMC Microbiol* 2013; **13**: 245 [PMID: 24195496 DOI: 10.1186/1471-2180-13-245]

274 **Smani Y**, Fàbrega A, Roca I, Sánchez-Encinales V, Vila J, Pachón J. Role of OmpA in the multidrug resistance phenotype of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2014; **58**: 1806-1808 [PMID: 24379205 DOI: 10.1128/AAC.02101-13]

275 **Lambert PA**. Bacterial resistance to antibiotics: modified target sites. *Adv Drug Deliv Rev* 2005; **57**: 1471-1485 [PMID: 15964098 DOI: 10.1016/j.addr.2005.04.003]

276 **Gehrlein M**, Leying H, Cullmann W, Wendt S, Opferkuch W. Imipenem resistance in Acinetobacter baumanii is due to altered penicillin-binding proteins. *Chemotherapy* 1991; **37**: 405-412 [PMID: 1760939]

277 **Cayô R**, Rodríguez MC, Espinal P, Fernández-Cuenca F, Ocampo-Sosa AA, Pascual A, Ayala JA, Vila J, Martínez-Martínez L. Analysis of genes encoding penicillin-binding proteins in clinical isolates of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2011; **55**: 5907-5913 [PMID: 21947403 DOI: 10.1128/AAC.00459-11]

278 **Vila J**, Ruiz J, Goñi P, Marcos A, Jimenez de Anta T. Mutation in the gyrA gene of quinolone-resistant clinical isolates of Acinetobacter baumannii. *Antimicrob Agents Chemother* 1995; **39**: 1201-1203 [PMID: 7625818 DOI: 10.1128/aac.39.5.1201]

279 **Taitt CR**, Leski TA, Stockelman MG, Craft DW, Zurawski DV, Kirkup BC, Vora GJ. Antimicrobial resistance determinants in Acinetobacter baumannii isolates taken from mili-

tary treatment facilities. *Antimicrob Agents Chemother* 2014; **58**: 767-781 [PMID: 24247131 DOI: 10.1128/aac.01897-13]
280 **Ribera A**, Ruiz J, Vila J. Presence of the Tet M determinant in a clinical isolate of Acinetobacter baumannii. *Antimicrob Agents Chemother* 2003; **47**: 2310-2312 [PMID: 12821485 DOI: 10.1128/aac.47.7.2310-2312.2003]
281 **Mak JK**, Kim MJ, Pham J, Tapsall J, White PA. Antibiotic resistance determinants in nosocomial strains of multidrug-resistant Acinetobacter baumannii. *J Antimicrob Chemother* 2009; **63**: 47-54 [PMID: 18988680 DOI: 10.1093/jac/dkn454]
282 **Yu YS**, Zhou H, Yang Q, Chen YG, Li LJ. Widespread occurrence of aminoglycoside resistance due to ArmA methylase in imipenem-resistant Acinetobacter baumannii isolates in China. *J Antimicrob Chemother* 2007; **60**: 454-455 [PMID: 17561497 DOI: 10.1093/jac/dkm208]
283 **Hong SB**, Shin KS, Ha J, Han K. Co-existence of blaOXA-23 and armA in multidrug-resistant Acinetobacter baumannii isolated from a hospital in South Korea. *J Med Microbiol* 2013; **62**: 836-844 [PMID: 23518656 DOI: 10.1099/jmm.0.055384-0]
284 **Karthikeyan K**, Thirunarayan MA, Krishnan P. Coexistence of blaOXA-23 with blaNDM-1 and armA in clinical isolates of Acinetobacter baumannii from India. *J Antimicrob Chemother* 2010; **65**: 2253-2254 [PMID: 20650909 DOI: 10.1093/jac/dkq273]
285 **Brigante G**, Migliavacca R, Bramati S, Motta E, Nucleo E, Manenti M, Migliorino G, Pagani L, Luzzaro F, Viganò FE. Emergence and spread of a multidrug-resistant Acinetobacter baumannii clone producing both the carbapenemase OXA-23 and the 16S rRNA methylase ArmA. *J Med Microbiol* 2012; **61**: 653-661 [PMID: 22282459 DOI: 10.1099/jmm.0.040980-0]
286 **Tada T**, Miyoshi-Akiyama T, Shimada K, Shimojima M, Kirikae T. Dissemination of 16S rRNA methylase ArmA-producing acinetobacter baumannii and emergence of OXA-72 carbapenemase coproducers in Japan. *Antimicrob Agents Chemother* 2014; **58**: 2916-2920 [PMID: 24550340 DOI: 10.1128/aac.01212-13]
287 **Carattoli A**. Importance of integrons in the diffusion of resistance. *Vet Res* 2001; **32**: 243-259 [PMID: 11432416]
288 **Mazel D**. Integrons: agents of bacterial evolution. *Nat Rev Microbiol* 2006; **4**: 608-620 [PMID: 16845431 DOI: 10.1038/nrmicro1462]
289 **Hall RM**, Collis CM, Kim MJ, Partridge SR, Recchia GD, Stokes HW. Mobile gene cassettes and integrons in evolution. *Ann N Y Acad Sci* 1999; **870**: 68-80 [PMID: 10415474]
290 **Gu B**, Tong M, Zhao W, Liu G, Ning M, Pan S, Zhao W. Prevalence and characterization of class I integrons among Pseudomonas aeruginosa and Acinetobacter baumannii isolates from patients in Nanjing, China. *J Clin Microbiol* 2007; **45**: 241-243 [PMID: 17122024 DOI: 10.1128/JCM.01318-06]
291 **Huang LY**, Chen TL, Lu PL, Tsai CA, Cho WL, Chang FY, Fung CP, Siu LK. Dissemination of multidrug-resistant, class 1 integron-carrying Acinetobacter baumannii isolates in Taiwan. *Clin Microbiol Infect* 2008; **14**: 1010-1019 [PMID: 19040472 DOI: 10.1111/j.1469-0691.2008.02077.x]
292 **Ploy MC**, Denis F, Courvalin P, Lambert T. Molecular characterization of integrons in Acinetobacter baumannii: description of a hybrid class 2 integron. *Antimicrob Agents Chemother* 2000; **44**: 2684-2688 [PMID: 10991844]
293 **Koeleman JG**, Stoof J, Van Der Bijl MW, Vandenbroucke-Grauls CM, Savelkoul PH. Identification of epidemic strains of Acinetobacter baumannii by integrase gene PCR. *J Clin Microbiol* 2001; **39**: 8-13 [PMID: 11136740 DOI: 10.1128/JCM.39.1.8-13.2001]
294 **Turton JF**, Kaufmann ME, Glover J, Coelho JM, Warner M, Pike R, Pitt TL. Detection and typing of integrons in epidemic strains of Acinetobacter baumannii found in the United Kingdom. *J Clin Microbiol* 2005; **43**: 3074-3082 [PMID: 16000417 DOI: 10.1128/JCM.43.7.3074-3082.2005]
295 **Gaur A**, Prakash P, Anupurba S, Mohapatra TM. Possible role of integrase gene polymerase chain reaction as an epidemiological marker: study of multidrug-resistant Acinetobacter baumannii isolated from nosocomial infections. *Int J Antimicrob Agents* 2007; **29**: 446-450 [PMID: 17270402 DOI: 10.1016/j.ijantimicag.2006.11.014]
296 **Gombac F**, Riccio ML, Rossolini GM, Lagatolla C, Tonin E, Monti-Bragadin C, Lavenia A, Dolzani L. Molecular characterization of integrons in epidemiologically unrelated clinical isolates of Acinetobacter baumannii from Italian hospitals reveals a limited diversity of gene cassette arrays. *Antimicrob Agents Chemother* 2002; **46**: 3665-3668 [PMID: 12384388 DOI: 10.1128/aac.46.11.3665-3668.2002]
297 **Ruiz J**, Navia MM, Casals C, Sierra JM, Jiménez De Anta MT, Vila J. Integron-mediated antibiotic multiresistance in Acinetobacter baumannii clinical isolates from Spain. *Clin Microbiol Infect* 2003; **9**: 907-911 [PMID: 14616677]
298 **Martinez-Freijo P**, Fluit AC, Schmitz FJ, Grek VS, Verhoef J, Jones ME. Class I integrons in Gram-negative isolates from different European hospitals and association with decreased susceptibility to multiple antibiotic compounds. *J Antimicrob Chemother* 1998; **42**: 689-696 [PMID: 10052890]
299 **Yang CM**, Lin MF, Lin CH, Huang YT, Hsu CT, Liou ML. Characterization of antimicrobial resistance patterns and integrons in human fecal Escherichia coli in Taiwan. *Jpn J Infect Dis* 2009; **62**: 177-181 [PMID: 19468175]
300 **Liu SY**, Lin JY, Chu C, Su LH, Lin TY, Chiu CH. Integron-associated imipenem resistance in Acinetobacter baumannii isolated from a regional hospital in Taiwan. *Int J Antimicrob Agents* 2006; **27**: 81-84 [PMID: 16359845 DOI: 10.1016/j.ijantimicag.2005.09.010]
301 **Chen YS**, Lin HH, Wu CH, Hsiao YS, Hsu NS, Chen YL. Colonization of a medical center in Southern Taiwan by epidemic strains of carbapenem- and multidrug-resistant Acinetobacter baumannii and the genetic organization of their integrons. *Jpn J Infect Dis* 2009; **62**: 155-157 [PMID: 19305060]
302 **Wu TL**, Ma L, Chang JC, Su LH, Chu C, Leu HS, Siu LK. Variable resistance patterns of integron-associated multidrug-resistant Acinetobacter baumannii isolates in a surgical intensive care unit. *Microb Drug Resist* 2004; **10**: 292-299 [PMID: 15650373]
303 **Mendes RE**, Castanheira M, Toleman MA, Sader HS, Jones RN, Walsh TR. Characterization of an integron carrying blaIMP-1 and a new aminoglycoside resistance gene, aac(6′)-31, and its dissemination among genetically unrelated clinical isolates in a Brazilian hospital. *Antimicrob Agents Chemother* 2007; **51**: 2611-2614 [PMID: 17470660 DOI: 10.1128/AAC.00838-06]
304 **Xu X**, Kong F, Cheng X, Yan B, Du X, Gai J, Ai H, Shi L, Iredell J. Integron gene cassettes in Acinetobacter spp. strains from South China. *Int J Antimicrob Agents* 2008; **32**: 441-445 [PMID: 18757181 DOI: 10.1016/j.ijantimicag.2008.05.014]
305 **Garnacho-Montero J**, Ortiz-Leyba C, Fernández-Hinojosa E, Aldabó-Pallás T, Cayuela A, Marquez-Vácaro JA, Garcia-Curiel A, Jiménez-Jiménez FJ. Acinetobacter baumannii ventilator-associated pneumonia: epidemiological and clinical findings. *Intensive Care Med* 2005; **31**: 649-655 [PMID: 15785929 DOI: 10.1007/s00134-005-2598-0]
306 **Lortholary O**, Fagon JY, Hoi AB, Slama MA, Pierre J, Giral P, Rosenzweig R, Gutmann L, Safar M, Acar J. Nosocomial acquisition of multiresistant Acinetobacter baumannii: risk factors and prognosis. *Clin Infect Dis* 1995; **20**: 790-796 [PMID: 7795075]
307 **Falagas ME**, Rafailidis PI. Attributable mortality of Acinetobacter baumannii: no longer a controversial issue. *Crit Care* 2007; **11**: 134 [PMID: 17543135 DOI: 10.1186/cc5911]
308 **Sunenshine RH**, Wright MO, Maragakis LL, Harris AD, Song X, Hebden J, Cosgrove SE, Anderson A, Carnell J, Jernigan DB, Kleinbaum DG, Perl TM, Standiford HC, Srinivasan

A. Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. *Emerg Infect Dis* 2007; **13**: 97-103 [PMID: 17370521 DOI: 10.3201/eid1301.060716]

309 **Grupper M**, Sprecher H, Mashiach T, Finkelstein R. Attributable mortality of nosocomial Acinetobacter bacteremia. *Infect Control Hosp Epidemiol* 2007; **28**: 293-298 [PMID: 17326019]

310 **Playford EG**, Craig JC, Iredell JR. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. *J Hosp Infect* 2007; **65**: 204-211 [PMID: 17254667 DOI: 10.1016/j.jhin.2006.11.010]

311 **Kwon KT**, Oh WS, Song JH, Chang HH, Jung SI, Kim SW, Ryu SY, Heo ST, Jung DS, Rhee JY, Shin SY, Ko KS, Peck KR, Lee NY. Impact of imipenem resistance on mortality in patients with Acinetobacter bacteraemia. *J Antimicrob Chemother* 2007; **59**: 525-530 [PMID: 17213265 DOI: 10.1093/jac/dkl499]

312 **Robenshtok E**, Paul M, Leibovici L, Fraser A, Pitlik S, Ostfeld I, Samra Z, Perez S, Lev B, Weinberger M. The significance of Acinetobacter baumannii bacteraemia compared with Klebsiella pneumoniae bacteraemia: risk factors and outcomes. *J Hosp Infect* 2006; **64**: 282-287 [PMID: 16930770 DOI: 10.1016/j.jhin.2006.06.025]

313 **Falagas ME**, Kasiakou SK, Rafailidis PI, Zouglakis G, Morfou P. Comparison of mortality of patients with Acinetobacter baumannii bacteraemia receiving appropriate and inappropriate empirical therapy. *J Antimicrob Chemother* 2006; **57**: 1251-1254 [PMID: 16627593 DOI: 10.1093/jac/dkl130]

314 **Turner PJ**, Greenhalgh JM. The activity of meropenem and comparators against Acinetobacter strains isolated from European hospitals, 1997-2000. *Clin Microbiol Infect* 2003; **9**: 563-567 [PMID: 12848736]

315 **Unal S**, Garcia-Rodriguez JA. Activity of meropenem and comparators against Pseudomonas aeruginosa and Acinetobacter spp. isolated in the MYSTIC Program, 2002-2004. *Diagn Microbiol Infect Dis* 2005; **53**: 265-271 [PMID: 16360550 DOI: 10.1016/j.diagmicrobio.2005.10.002]

316 **Tognim MC**, Andrade SS, Silbert S, Gales AC, Jones RN, Sader HS. Resistance trends of Acinetobacter spp. in Latin America and characterization of international dissemination of multi-drug resistant strains: five-year report of the SENTRY Antimicrobial Surveillance Program. *Int J Infect Dis* 2004; **8**: 284-291 [PMID: 15325597 DOI: 10.1016/j.ijid.2003.11.009]

317 **Landman D**, Bratu S, Kochar S, Panwar M, Trehan M, Doymaz M, Quale J. Evolution of antimicrobial resistance among Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae in Brooklyn, NY. *J Antimicrob Chemother* 2007; **60**: 78-82 [PMID: 17490999 DOI: 10.1093/jac/dkm129]

318 **Mai MH**, Tsai HC, Lee SS, Wang YH, Chen YS, Wann SR, Liu YC. Multidrug-resistant Acinetobacter baumannii in ventilator-associated pneumonia at a medical center in southern Taiwan. *J Microbiol Immunol Infect* 2007; **40**: 401-405 [PMID: 17932599]

319 **Chopra T**, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, Chaudary K, Lephart P, Slim J, Hothi J, Ahmed H, Pogue JM, Zhao JJ, Kaye KS. Epidemiology of bloodstream infections caused by Acinetobacter baumannii and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes. *Antimicrob Agents Chemother* 2013; **57**: 6270-6275 [PMID: 24100492 DOI: 10.1128/AAC.01520-13]

320 **Wong TH**, Tan BH, Ling ML, Song C. Multi-resistant Acinetobacter baumannii on a burns unit--clinical risk factors and prognosis. *Burns* 2002; **28**: 349-357 [PMID: 12052373]

321 **Sheng WH**, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, Lau YJ, Wang LH, Liu KS, Tsai TY, Lin SY, Hsu MS, Hsu LY, Chang SC. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant Acinetobacter baumannii. *Int J Infect Dis* 2010; **14**: e764-e769 [PMID: 20646946 DOI: 10.1016/j.ijid.2010.02.2254]

322 **Gkrania-Klotsas E**, Hershow RC. Colonization or infection with multidrug-resistant Acinetobacter baumannii may be an independent risk factor for increased mortality. *Clin Infect Dis* 2006; **43**: 1224-1225 [PMID: 17029151]

323 **Giske CG**, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother* 2008; **52**: 813-821 [PMID: 18070961 DOI: 10.1128/AAC.01169-07]

324 **Payne DJ**, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* 2007; **6**: 29-40 [PMID: 17159923 DOI: 10.1038/nrd2201]

325 **Rebmann T**, Rosenbaum PA. Preventing the transmission of multidrug-resistant Acinetobacter baumannii: an executive summary of the Association for Professionals in infection control and epidemiology's elimination guide. *Am J Infect Control* 2011; **39**: 439-441 [PMID: 21420758 DOI: 10.1016/j.ajic.2010.08.015]

326 **Dy ME**, Nord JA, LaBombardi VJ, Kislak JW. The emergence of resistant strains of Acinetobacter baumannii: clinical and infection control implications. *Infect Control Hosp Epidemiol* 1999; **20**: 565-567 [PMID: 10466561 DOI: 10.1086/501673]

327 **Akalin H**, Ozakin C, Gedikoglu S. Epidemiology of Acinetobacter baumannii in a university hospital in Turkey. *Infect Control Hosp Epidemiol* 2006; **27**: 404-408 [PMID: 16622820 DOI: 10.1086/503349]

328 **Ho PL**, Ho AY, Chow KH, Lai EL, Ching P, Seto WH. Epidemiology and clonality of multidrug-resistant Acinetobacter baumannii from a healthcare region in Hong Kong. *J Hosp Infect* 2010; **74**: 358-364 [PMID: 20153548 DOI: 10.1016/j.jhin.2009.10.015]

329 **Kraniotaki E**, Manganelli R, Platsouka E, Grossato A, Paniara O, Palù G. Molecular investigation of an outbreak of multidrug-resistant Acinetobacter baumannii, with characterisation of class 1 integrons. *Int J Antimicrob Agents* 2006; **28**: 193-199 [PMID: 16904293 DOI: 10.1016/j.ijantimicag.2006.04.016]

330 **Koeleman JG**, Parlevliet GA, Dijkshoorn L, Savelkoul PH, Vandenbroucke-Grauls CM. Nosocomial outbreak of multiresistant Acinetobacter baumannii on a surgical ward: epidemiology and risk factors for acquisition. *J Hosp Infect* 1997; **37**: 113-123 [PMID: 9364260]

331 **Gandra S**, Braykov N, Laxminarayan R. East North Central region has the highest prevalence of vancomycin-resistant Enterococcus faecalis in the United States. *Infect Control Hosp Epidemiol* 2013; **34**: 443-445 [PMID: 23466924 DOI: 10.1086/669872]

332 **Barbut F**, Yezli S, Mimoun M, Pham J, Chaouat M, Otter JA. Reducing the spread of Acinetobacter baumannii and methicillin-resistant Staphylococcus aureus on a burns unit through the intervention of an infection control bundle. *Burns* 2013; **39**: 395-403 [PMID: 22884127 DOI: 10.1016/j.burns.2012.07.007]

333 **Kuo HY**, Chang KC, Kuo JW, Yueh HW, Liou ML. Imipenem: a potent inducer of multidrug resistance in Acinetobacter baumannii. *Int J Antimicrob Agents* 2012; **39**: 33-38 [PMID: 21996406 DOI: 10.1016/j.ijantimicag.2011.08.016]

334 **Lautenbach E**, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, Kim M. Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. *Infect Control Hosp Epidemiol* 2009; **30**: 1186-1192 [PMID: 19860563 DOI: 10.1086/648450]

335 **Cisneros JM**, Rodríguez-Baño J. Nosocomial bacteremia due to Acinetobacter baumannii: epidemiology, clinical features and treatment. *Clin Microbiol Infect* 2002; **8**: 687-693 [PMID: 12445005]

336 **Gordon NC**, Wareham DW. A review of clinical and microbiological outcomes following treatment of infections

involving multidrug-resistant Acinetobacter baumannii with tigecycline. *J Antimicrob Chemother* 2009; **63**: 775-780 [PMID: 19158109 DOI: 10.1093/jac/dkn555]

337 **Smolyakov R**, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, Rimar D, Almog Y, Gilad J. Nosocomial multidrug resistant Acinetobacter baumannii bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. *J Hosp Infect* 2003; **54**: 32-38 [PMID: 12767844 DOI: 10.1016/s0195-6701(03)00046-x]

338 **Chu H**, Zhao L, Wang M, Liu Y, Gui T, Zhang J. Sulbactam-based therapy for Acinetobacter baumannii infection: a systematic review and meta-analysis. *Braz J Infect Dis* 2013; **17**: 389-394 [PMID: 23602463 DOI: 10.1016/j.bjid.2012.10.029]

339 **Hiraki Y**, Yoshida M, Masuda Y, Inoue D, Tsuji Y, Kamimura H, Karube Y, Takaki K, Kawano F. Successful treatment of skin and soft tissue infection due to carbapenem-resistant Acinetobacter baumannii by ampicillin-sulbactam and meropenem combination therapy. *Int J Infect Dis* 2013; **17**: e1234-e1236 [PMID: 23791858 DOI: 10.1016/j.ijid.2013.05.002]

340 **Kuo LC**, Lai CC, Liao CH, Hsu CK, Chang YL, Chang CY, Hsueh PR. Multidrug-resistant Acinetobacter baumannii bacteraemia: clinical features, antimicrobial therapy and outcome. *Clin Microbiol Infect* 2007; **13**: 196-198 [PMID: 17328733 DOI: 10.1111/j.1469-0691.2006.01601.x]

341 **Kalin G**, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. *Infection* 2014; **42**: 37-42 [PMID: 23828559 DOI: 10.1007/s15010-013-0495-y]

342 **Pachón-Ibáñez ME**, Jiménez-Mejías ME, Pichardo C, Llanos AC, Pachón J. Activity of tigecycline (GAR-936) against Acinetobacter baumannii strains, including those resistant to imipenem. *Antimicrob Agents Chemother* 2004; **48**: 4479-4481 [PMID: 15504889 DOI: 10.1128/AAC.48.11.4479-4481.2004]

343 **Bantar C**, Schell C, Posse G, Limansky A, Ballerini V, Mobilia L. Comparative time-kill study of doxycycline, tigecycline, sulbactam, and imipenem against several clones of Acinetobacter baumannii. *Diagn Microbiol Infect Dis* 2008; **61**: 309-314 [PMID: 18375084 DOI: 10.1016/j.diagmicrobio.2008.02.014]

344 **Koomanachai P**, Kim A, Nicolau DP. Pharmacodynamic evaluation of tigecycline against Acinetobacter baumannii in a murine pneumonia model. *J Antimicrob Chemother* 2009; **63**: 982-987 [PMID: 19279050 DOI: 10.1093/jac/dkp056]

345 **Anthony KB**, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. *Clin Infect Dis* 2008; **46**: 567-570 [PMID: 18199038 DOI: 10.1086/526775]

346 **Pichardo C**, Pachón-Ibañez ME, Docobo-Perez F, López-Rojas R, Jiménez-Mejías ME, Garcia-Curiel A, Pachon J. Efficacy of tigecycline vs. imipenem in the treatment of experimental Acinetobacter baumannii murine pneumonia. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 527-531 [PMID: 20182760 DOI: 10.1007/s10096-010-0890-6]

347 **Liao CH**, Kung HC, Hsu GJ, Lu PL, Liu YC, Chen CM, Lee CM, Sun W, Jang TN, Chiang PC, Cheng YJ, Lin HC, Shi ZY, Wang LS, Chuang YC, Tsao SM, Lu CT, Liu JW, Huang CH, Hsueh PR. In-vitro activity of tigecycline against clinical isolates of Acinetobacter baumannii in Taiwan determined by the broth microdilution and disk diffusion methods. *Int J Antimicrob Agents* 2008; **32** Suppl 3: S192-S196 [PMID: 19013354 DOI: 10.1016/s0924-8579(08)70027-x]

348 **Curcio D**, Fernández F. Tigecycline for Acinetobacter baumannii infection: other considerations. *Clin Infect Dis* 2008; **46**: 1797-1798; author reply 1798-1799 [PMID: 18462123 DOI: 10.1086/588051]

349 **Chuang YC**, Cheng CY, Sheng WH, Sun HY, Wang JT, Chen YC, Chang SC. Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant Acinetobacter baumannii in a critical setting: a matched cohort analysis. *BMC Infect Dis* 2014; **14**: 102 [PMID: 24564226 DOI: 10.1186/1471-2334-14-102]

350 **Yahav D**, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* 2011; **66**: 1963-1971 [PMID: 21685488 DOI: 10.1093/jac/dkr242]

351 **Scheetz MH**, Qi C, Warren JR, Postelnick MJ, Zembower T, Obias A, Noskin GA. In vitro activities of various antimicrobials alone and in combination with tigecycline against carbapenem-intermediate or -resistant Acinetobacter baumannii. *Antimicrob Agents Chemother* 2007; **51**: 1621-1626 [PMID: 17307973 DOI: 10.1128/AAC.01099-06]

352 **Lee YT**, Tsao SM, Hsueh PR. Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant Acinetobacter baumannii infections. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 1211-1220 [PMID: 23553594 DOI: 10.1007/s10096-013-1870-4]

353 **Moland ES**, Craft DW, Hong SG, Kim SY, Hachmeister L, Sayed SD, Thomson KS. In vitro activity of tigecycline against multidrug-resistant Acinetobacter baumannii and selection of tigecycline-amikacin synergy. *Antimicrob Agents Chemother* 2008; **52**: 2940-2942 [PMID: 18519722 DOI: 10.1128/AAC.01581-07]

354 **Liu JW**, Wang LS, Cheng YJ, Hsu GJ, Lu PL, Liu YC, Chen CM, Lee CM, Sun W, Jang TN, Chiang PC, Chuang YC, Lin HC, Shi ZY, Kung HC, Huang CH, Tsao SM, Lu CT, Liao CH, Hsueh PR. In-vitro activity of tigecycline against clinical isolates of Acinetobacter baumannii in Taiwan. *Int J Antimicrob Agents* 2008; **32** Suppl 3: S188-S191 [PMID: 19013353 DOI: 10.1016/s0924-8579(08)70026-8]

355 **Hornsey M**, Loman N, Wareham DW, Ellington MJ, Pallen MJ, Turton JF, Underwood A, Gaulton T, Thomas CP, Doumith M, Livermore DM, Woodford N. Whole-genome comparison of two Acinetobacter baumannii isolates from a single patient, where resistance developed during tigecycline therapy. *J Antimicrob Chemother* 2011; **66**: 1499-1503 [PMID: 21565804 DOI: 10.1093/jac/dkr168]

356 **Navon-Venezia S**, Leavitt A, Carmeli Y. High tigecycline resistance in multidrug-resistant Acinetobacter baumannii. *J Antimicrob Chemother* 2007; **59**: 772-774 [PMID: 17353223 DOI: 10.1093/jac/dkm018]

357 **Cai Y**, Chai D, Wang R, Liang B, Bai N. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. *J Antimicrob Chemother* 2012; **67**: 1607-1615 [PMID: 22441575 DOI: 10.1093/jac/dks084]

358 **Chang KC**, Lin MF, Lin NT, Wu WJ, Kuo HY, Lin TY, Yang TL, Chen YC, Liou ML. Clonal spread of multidrug-resistant Acinetobacter baumannii in eastern Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 37-42 [PMID: 22154678 DOI: 10.1016/j.jmii.2011.09.019]

359 **Karaiskos I**, Galani L, Baziaka F, Giamarellou H. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: a literature review. *Int J Antimicrob Agents* 2013; **41**: 499-508 [PMID: 23507414 DOI: 10.1016/j.ijantimicag.2013.02.006]

360 **Lu Q**, Luo R, Bodin L, Yang J, Zahr N, Aubry A, Golmard JL, Rouby JJ. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. *Anesthesiology* 2012; **117**: 1335-1347 [PMID: 23132092 DOI: 10.1097/ALN.0b013e31827515de]

361 **Lin CC**, Liu TC, Kuo CF, Liu CP, Lee CM. Aerosolized colistin for the treatment of multidrug-resistant Acinetobacter baumannii pneumonia: experience in a tertiary care hospital in northern Taiwan. *J Microbiol Immunol Infect* 2010; **43**: 323-331

[PMID: 20688293 DOI: 10.1016/S1684-1182(10)60050-3]
362 **Adams MD**, Nickel GC, Bajaksouzian S, Lavender H, Murthy AR, Jacobs MR, Bonomo RA. Resistance to colistin in Acinetobacter baumannii associated with mutations in the PmrAB two-component system. *Antimicrob Agents Chemother* 2009; **53**: 3628-3634 [PMID: 19528270 DOI: 10.1128/AAC.00284-09]
363 **Beceiro A**, Llobet E, Aranda J, Bengoechea JA, Doumith M, Hornsey M, Dhanji H, Chart H, Bou G, Livermore DM, Woodford N. Phosphoethanolamine modification of lipid A in colistin-resistant variants of Acinetobacter baumannii mediated by the pmrAB two-component regulatory system. *Antimicrob Agents Chemother* 2011; **55**: 3370-3379 [PMID: 21576434 DOI: 10.1128/AAC.00079-11]
364 **Karaoglan I**, Zer Y, Bosnak VK, Mete AO, Namiduru M. In vitro synergistic activity of colistin with tigecycline or β-lactam antibiotic/β-lactamase inhibitor combinations against carbapenem-resistant Acinetobacter baumannii. *J Int Med Res* 2013; **41**: 1830-1837 [PMID: 24265334 DOI: 10.1177/0300060513496172]
365 **Liang W**, Liu XF, Huang J, Zhu DM, Li J, Zhang J. Activities of colistin- and minocycline-based combinations against extensive drug resistant Acinetobacter baumannii isolates from intensive care unit patients. *BMC Infect Dis* 2011; **11**: 109 [PMID: 21521536 DOI: 10.1186/1471-2334-11-109.]
366 **Aydemir H**, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, Kokturk F, Ornek T, Celebi G. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Epidemiol Infect* 2013; **141**: 1214-1222 [PMID: 22954403 DOI: 10.1017/S095026881200194X]
367 **Durante-Mangoni E**, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, Bassetti M, Malacarne P, Petrosillo N, Galdieri N, Mocavero P, Corcione A, Viscoli C, Zarrilli R, Gallo C, Utili R. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. *Clin Infect Dis* 2013; **57**: 349-358 [PMID: 23616495 DOI: 10.1093/cid/cit253]
368 **Giannouli M**, Di Popolo A, Durante-Mangoni E, Bernardo M, Cuccurullo S, Amato G, Tripodi MF, Triassi M, Utili R, Zarrilli R. Molecular epidemiology and mechanisms of rifampicin resistance in Acinetobacter baumannii isolates from Italy. *Int J Antimicrob Agents* 2012; **39**: 58-63 [PMID: 22055530 DOI: 10.1016/j.ijantimicag.2011.09.016]
369 **Batirel A**, Balkan II, Karabay O, Agalar C, Akalin S, Alici O, Alp E, Altay FA, Altin N, Arslan F, Aslan T, Bekiroglu N, Cesur S, Celik AD, Dogan M, Durdu B, Duygu F, Engin A, Engin DO, Gonen I, Guclu E, Guven T, Hatipoglu CA, Hosoglu S, Karahocagil MK, Kilic AU, Ormen B, Ozdemir D, Ozer S, Oztoprak N, Sezak N, Turhan V, Turker N, Yilmaz H. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1311-1322 [PMID: 24532009 DOI: 10.1007/s10096-014-2070-6]
370 **Mutlu Yilmaz E**, Sunbul M, Aksoy A, Yilmaz H, Guney AK, Guvenc T. Efficacy of tigecycline/colistin combination in a pneumonia model caused by extensively drug-resistant Acinetobacter baumannii. *Int J Antimicrob Agents* 2012; **40**: 332-336 [PMID: 22831842 DOI: 10.1016/j.ijantimicag.2012.06.003]
371 **Wareham DW**, Gordon NC, Hornsey M. In vitro activity of teicoplanin combined with colistin versus multidrug-resistant strains of Acinetobacter baumannii. *J Antimicrob Chemother* 2011; **66**: 1047-1051 [PMID: 21393131 DOI: 10.1093/jac/dkr069]
372 **Hornsey M**, Phee L, Longshaw C, Wareham DW. In vivo efficacy of telavancin/colistin combination therapy in a Galleria mellonella model of Acinetobacter baumannii infection. *Int J Antimicrob Agents* 2013; **41**: 285-287 [PMID: 23312607 DOI: 10.1016/j.ijantimicag.2012.11.013]
373 **Principe L**, Capone A, Mazzarelli A, D'Arezzo S, Bordi E, Di Caro A, Petrosillo N. In vitro activity of doripenem in combination with various antimicrobials against multidrug-resistant Acinetobacter baumannii: possible options for the treatment of complicated infection. *Microb Drug Resist* 2013; **19**: 407-414 [PMID: 23659601 DOI: 10.1089/mdr.2012.0250]
374 **López-Cortés LE**, Cisneros JM, Fernández-Cuenca F, Bou G, Tomás M, Garnacho-Montero J, Pascual A, Martínez-Martínez L, Vila J, Pachón J, Rodríguez Baño J. Monotherapy versus combination therapy for sepsis due to multidrug-resistant Acinetobacter baumannii: analysis of a multicentre prospective cohort. *J Antimicrob Chemother* 2014; **69**: 3119-3126 [PMID: 24970742 DOI: 10.1093/jac/dku233]
375 **Zavascki AP**, Carvalhaes CG, Picão RC, Gales AC. Multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii: resistance mechanisms and implications for therapy. *Expert Rev Anti Infect Ther* 2010; **8**: 71-93 [PMID: 20014903]
376 **Naas T**, Cuzon G, Bogaerts P, Glupczynski Y, Nordmann P. Evaluation of a DNA microarray (Check-MDR CT102) for rapid detection of TEM, SHV, and CTX-M extended-spectrum β-lactamases and of KPC, OXA-48, VIM, IMP, and NDM-1 carbapenemases. *J Clin Microbiol* 2011; **49**: 1608-1613 [PMID: 21325547 DOI: 10.1128/JCM.02607-10]
377 **Cuzon G**, Naas T, Bogaerts P, Glupczynski Y, Nordmann P. Evaluation of a DNA microarray for the rapid detection of extended-spectrum β-lactamases (TEM, SHV and CTX-M), plasmid-mediated cephalosporinases (CMY-2-like, DHA, FOX, ACC-1, ACT/MIR and CMY-1-like/MOX) and carbapenemases (KPC, OXA-48, VIM, IMP and NDM). *J Antimicrob Chemother* 2012; **67**: 1865-1869 [PMID: 22604450 DOI: 10.1093/jac/dks156]
378 **Luh KT**, Hsueh PR, Teng LJ, Pan HJ, Chen YC, Lu JJ, Wu JJ, Ho SW. Quinupristin-dalfopristin resistance among gram-positive bacteria in Taiwan. *Antimicrob Agents Chemother* 2000; **44**: 3374-3380 [PMID: 11083643 DOI: 10.1128/aac.44.12.3374-3380.2000]
379 **Bals R**. Epithelial antimicrobial peptides in host defense against infection. *Respir Res* 2000; **1**: 141-150 [PMID: 11667978]
380 **Reddy KV**, Yedery RD, Aranha C. Antimicrobial peptides: premises and promises. *Int J Antimicrob Agents* 2004; **24**: 536-547 [PMID: 15555874 DOI: 10.1016/j.ijantimicag.2004.09.005]
381 **Izadpanah A**, Gallo RL. Antimicrobial peptides. *J Am Acad Dermatol* 2005; **52**: 381-390; quiz 391-392 [PMID: 15761415 DOI: 10.1016/j.jaad.2004.08.026]
382 **Moffatt JH**, Harper M, Mansell A, Crane B, Fitzsimons TC, Nation RL, Li J, Adler B, Boyce JD. Lipopolysaccharide-deficient Acinetobacter baumannii shows altered signaling through host Toll-like receptors and increased susceptibility to the host antimicrobial peptide LL-37. *Infect Immun* 2013; **81**: 684-689 [PMID: 23250952 DOI: 10.1128/IAI.01362-12]
383 **Feng X**, Sambanthamoorthy K, Palys T, Paranavitana C. The human antimicrobial peptide LL-37 and its fragments possess both antimicrobial and antibiofilm activities against multidrug-resistant Acinetobacter baumannii. *Peptides* 2013; **49**: 131-137 [PMID: 24071034 DOI: 10.1016/j.peptides.2013.09.007]
384 **Weinstock GM**. Genomic approaches to studying the human microbiota. *Nature* 2012; **489**: 250-256 [PMID: 22972298]
385 **Proctor LM**. The Human Microbiome Project in 2011 and beyond. *Cell Host Microbe* 2011; **10**: 287-291 [PMID: 22018227 DOI: 10.1016/j.chom.2011.10.001]
386 **Cabrera-Rubio R**, Garcia-Núñez M, Setó L, Antó JM, Moya A, Monsó E, Mira A. Microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary dis-

ease. *J Clin Microbiol* 2012; **50**: 3562-3568 [PMID: 22915614 DOI: 10.1128/JCM.00767-12]

387 **Giannouli M**, Tomasone F, Agodi A, Vahaboglu H, Daoud Z, Triassi M, Tsakris A, Zarrilli R. Molecular epidemiology of carbapenem-resistant Acinetobacter baumannii strains in intensive care units of multiple Mediterranean hospitals. *J Antimicrob Chemother* 2009; **63**: 828-830 [PMID: 19223304 DOI: 10.1093/jac/dkp032]

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