

## *Acinetobacter baumannii*: An emerging pathogenic threat to public health

Suresh G Joshi, Geetanjali M Litake

Suresh G Joshi, Surgical and Nosocomial Infections Research Program, Drexel University College of Medicine, Philadelphia, PA 19102, United States

Geetanjali M Litake, Department of Biotechnology, Modern College, University of Pune affiliate, Pune 411007, India

**Author contributions:** Both authors have approved the final version of this manuscript and contributed to analysis and interpretation of data; Joshi SG contributed to the conception and design of the manuscript, acquisition of data, drafting the manuscript for intellectual content and modified version; Litake GM contributed to developing rough draft of the manuscript.

**Correspondence to:** Suresh G Joshi, MD, PhD, Surgical and Nosocomial Infections Research Program, Drexel University College of Medicine, 245 North 15<sup>th</sup> Street, Suite 7150, Mail 413, Philadelphia, PA 19102,

United States. [suresh.joshi@drexelmed.edu](mailto:suresh.joshi@drexelmed.edu)

Telephone: +1-215-7628431 Fax: +1-215-7628389

Received: June 21, 2013 Revised: July 26, 2013

Accepted: August 4, 2013

Published online: August 25, 2013

### Abstract

Over the last three decades, *Acinetobacter* has gained importance as a leading nosocomial pathogen, partly due to its impressive genetic capabilities to acquire resistance and partly due to high selective pressure, especially in critical care units. This low-virulence organism has turned into a multidrug resistant pathogen and now alarming healthcare providers worldwide. *Acinetobacter baumannii* (*A. baumannii*) is a major species, contributing about 80% of all *Acinetobacter* hospital-acquired infections. It disseminates antibiotic resistance by virtue of its extraordinary ability to accept or donate resistance plasmids. The procedures for breaking the route of transmission are still proper hand washing and personal hygiene (both the patient and the healthcare professional), reducing patient's biofilm burden from skin, and judicious use of antimicrobial agents. The increasing incidence of extended-spectrum beta-lactamases and carbapenemases in *A. baumannii* leaves almost no cure for these "bad bugs".

To control hospital outbreaks of multidrug resistant-*Acinetobacter* infection, we need to contain their dissemination or require new drugs or a rational combination therapy. The optimal treatment for multidrug-resistant *A. baumannii* infection has not been clearly established, and empirical therapy continues to require knowledge of susceptibility patterns of isolates from one's own institution. This review mainly focused on general features and introduction to *A. baumannii* and its epidemiological status, potential sources of infection, risk factors, and strategies to control infection to minimize spread.

© 2013 Baishideng. All rights reserved.

**Key words:** *Acinetobacter*; *Acinetobacter baumannii*; Biofilm; Combination therapy; Hospital-acquired infection; Intensive care unit; Multidrug resistance; Nosocomial Pathogen; Risk factor

**Core tip:** *Acinetobacter*, is Gram-negative cocco-bacilli, originally regarded as low virulence bacteria, adopted now with increasing incidences, and recognized as a significant healthcare-associated multidrug-resistant classical pathogen. *Acinetobacter baumannii* (*A. baumannii*) accounts for nearly 80% of reported *Acinetobacter* infections. *A. baumannii* resist desiccation, and survive for several months on animate and inanimate surfaces. It has excellent colonizing potential, and contact transmission is a big challenge intermittent as well as endemic outbreaks. Strong biofilm formation is a part of virulence pathogenesis strategies of this organisms, and elimination of the identified source often require multiple interventions. This review mainly discusses on relevant epidemiological features of *A. baumannii*.

Joshi SG, Litake GM. *Acinetobacter baumannii*: An emerging pathogenic threat to public health. *World J Clin Infect Dis* 2013; 3(3): 25-36 Available from: URL: <http://www.wjgnet.com/2220-3176/full/v3/i3/25.htm> DOI: <http://dx.doi.org/10.5495/wjcid.v3.i3.25>

## IMPORTANCE

Once documented as a pathogen with low virulence, *Acinetobacter* is currently an important etiological agent of nosocomial infections, including hospital-acquired pneumonia and ventilator-associated pneumonia in patients admitted to intensive care units (ICUs), wound infections from war, and natural disasters such as a tsunami<sup>[1-3]</sup>. The National Nosocomial Infections Surveillance System reported a significant increase in the proportion of *Acinetobacter* among all Gram-negative aerobes during the 17 years of the study period (1986 through 2003)<sup>[2]</sup>. *Acinetobacter* was the only pathogen showing consistently increasing incidence in nosocomial pneumonias, and *Acinetobacter baumannii* (*A. baumannii*) was a major species among reported causes of nosocomial pneumonia<sup>[3]</sup>.

### Taxonomical aspect

The Gram-negative, non-fermentative aerobic bacteria which now recognized as belonging to the genus *Acinetobacter* have in the past been classified under various generic names. The genus *Acinetobacter* is now classified in the family *Moraxillaceae*, which includes *Moraxella*, *Acinetobacter*, *Psychrobacter*, and related organisms<sup>[4]</sup>. The genus *Acinetobacter* includes *Gram-negative coccobacilli* that have a G + C content of 39-47 mol% and that are strictly aerobic, non-motile, catalase-positive, and oxidase-negative. The negative oxidase test is important for rapid presumptive identification to differentiate the genus *Acinetobacter* from other similar non-fermentative organisms. But the transformation assay of Juni is the only test considered to be an unambiguous identification test for the genus *Acinetobacter*<sup>[5]</sup>. Most *Acinetobacter* species are non-fastidious and can be easily grown on simple microbiological media. Although variants appear, typical colonies are smooth, domed shaped pale yellow to grayish, about 2 mm with entire edge. Most species grow at ambient temperature, and pathogenic species such as *A. baumannii* grow well at 37 °C. Enrichment medium such as Leeds selective medium as occasionally use, and are helpful in recovery of isolates from complex samples<sup>[6]</sup>.

The genus *Acinetobacter* encompasses at least 25 DNA groups (genospecies) identified by DNA-DNA hybridization, 23 of which have been officially validated<sup>[7-10]</sup>. A recently submitted species of *Acinetobacter nosocomialis* (*A. nosocomialis*) and *A. pittii* are included in taxonomic nomenclature. *Acinetobacter* uses a wide variety of organic compounds as a carbon sources. This property has been used in developing the identification system for this organism. It is often difficult in clinical laboratories to differentiate the isolates of *Acinetobacter* at the species level according to their phenotypic characteristics<sup>[8]</sup>, and can be inadequate for species confirmation, and should be used with caution. Automated systems available for distinguishing Gram-negative pathogens can identify *Acinetobacter* species but have limitations. *A. baumannii*, *Acinetobacter calcoaceticus* (*A. calcoaceticus*), genomic species 3, and 13TU are closely related and formally grouped as *A. baumannii-A. calcoaceticus* (Abc) complex (recently species 3 and 13TU

are referred as *A. pittii* and *A. nosocomialis*, respectively). Molecular characterization, particularly 16S rRNA gene sequence analysis, can be of great help to resolve matters of dispute. Looking at the global dissemination of international clones, and their involvement in outbreaks, the rapid and discriminating genotyping methods are required for delineation of such clonal lineages<sup>[11]</sup>. Among the most common methods that are currently used involves pulse-field gel electrophoresis, amplified fragment length polymorphism, single locus genotyping, trilocus sequence-based typing, multi-locus sequence typing such as PubMLST, Pasteur's MLST, multi-locus variable-number tandem-repeats, resistance island typing, PCR with electrospray ionization mass spectrometry, next-generation whole genome sequencing, and PCR-based replicon of plasmid DNA. Most of these genotyping methods are not routinely used in hospitals and not cost effective, but extremely useful for to establish clonal relationships of the isolates and their taxonomical classification<sup>[11-15]</sup>.

### Habitat and colonization

Although *Acinetobacter* has emerged as an important pathogen, little is known about its natural reservoirs and habitat. Pathogenic members of the genus *Acinetobacter* contribute to the normal flora of human skin, upper respiratory tract, and gastrointestinal tract. The clinical consequences of *Acinetobacter* infections range from minimal to moderate to severe. *A. baumannii*, along with two other genetically closely related species (genomic species 3 and 13TU), is almost exclusively associated with human infection and is phenotypically difficult to differentiate routinely in clinical laboratories. Hence, the group is known as *A. baumannii-A. calcoaceticus*-complex (Abc-complex), and is often regarded *A. baumannii* in clinical practice as<sup>[16,17]</sup>. Although many consider *A. baumannii* to be ubiquitous, not everyone agrees. It is considered to be commensal with humans, and colonization is well documented. Therefore, the switch from colonization to infection is more favorable than it would be from more distant environmental sources<sup>[10]</sup>. Other species that are occasionally isolated from clinical samples are *A. calcoaceticus*, *A. hemolyticus*, *Acinetobacter johnsonii* (*A. johnsonii*), *Acinetobacter lwoffii*, and *Acinetobacter ursingii*.

## EPIDEMIOLOGICAL ASPECT

*Acinetobacter species* account for a substantial proportion of epidemic and endemic nosocomial infections and occasional sporadic outbreaks<sup>[14,16,18,19]</sup>. Geographically distant outbreaks are being studied for their ancestral genetic pool and clonal lineage. Multilocus sequence typing analysis recognized I to III international clones, corresponds to their clonal complexes, and many of the isolates causing outbreaks are suspected phylogenetically to be closely related with these clonal groups<sup>[20]</sup>. It can cause a wide array of infections such as respiratory tract infections, bloodstream infections, urinary tract infec-

tions, meningitis, endocarditis, and wound infections. In a recent report, 6 out of 7 patients with *Acinetobacter* bloodstream infections found *A. baumannii* colonizing their gastrointestinal tract<sup>[21]</sup>. *A. baumannii* is a prevalent species that causes epidemic outbreaks of nosocomial *Acinetobacter* infections<sup>[17,22-24]</sup>. Although there are mixed opinions, *A. baumannii* is usually reported to have a known natural habitat around patient population and in healthcare facilities and is occasionally isolated from environmental samples such as soil and water. *A. baumannii* is an excellent colonizer and is known to form biofilms. Furthermore, the reports demonstrate a positive correlation between biofilm formation capabilities and the multidrug resistance (MDR) status of *A. baumannii*. Such phenotypes have the ability to mediate outbreaks<sup>[25]</sup>. The multifactorial nature of the pathogenicity of *A. baumannii* has been documented recently and various models are proposed, and the involvement the presence and expression of exoproteases and exopolysaccharides (mediating biofilms), iron acquisition resistance to serum, resistance to desiccation, adherence and colonization, epithelial cell invasion and extraordinary ability to acquire foreign genetic material through lateral transfer for own survival, are elaborated as virulence attributes<sup>[26-31]</sup>. *A. baumannii* survives for a relatively long time in environments such as dry animate and inanimate surfaces and, when conditions are favorable, leads to outbreaks. The exact natural habitat of many of the *Acinetobacter* species is yet to be fully understood and may require intense efforts to identify.

Towner describes that depending on the site of isolation and the population of species or strains involved, *Acinetobacter* can be broadly categorized into three groups<sup>[10]</sup>: (1) MDR isolates capable of colonizing and infecting hospitalized patients, usually mediating hospital outbreaks. Generally these are *A. baumannii*. The isolates usually belong to a single clone or limited clones. Intensive care units are the depots for such outbreaks (occasionally other units mediate their spread as well); and (2) Relatively less resistant, less virulent strains that occasionally cause outbreaks. These isolates can be a part of normal skin flora of humans or animals or are associated with food spoilage<sup>[10,32]</sup>. Examples of such isolates are *A. johnsonii*, *A. hwoffii*, and *A. radioresistens*<sup>[33]</sup>. Environmental sources of isolate that are sensitive to many routine antibiotics and rarely cause outbreaks. *A. calcoaceticus* is a classic example. Infection control practices are therefore reserved mainly for the resistant isolates, which are usually *A. baumannii*-complex members. The patterns of spread of these members are also peculiar and can be correlated to strains causing outbreaks. In many European and Asian hospitals, the clonal spread (single clone) of *A. baumannii* has been reported either in a single hospital or in multiple hospitals and the strain was susceptible only to colistin and tigecycline<sup>[34,35]</sup>. Epidemiological typing methods are often helpful in delineating their dissemination and the strains involved in an outbreak and can differentiate epidemic outbreaks from sporadic strains. Thus, overall diversity of habitat, predilection to accumulate antimicrobial resistance,

resistance to desiccation, ability to form biofilm, and propensity to cause hospital infection outbreaks make *Acinetobacter* an remarkable microorganism.

*A. baumannii* strains are generally more resistant than other species of this genus and often express a MDR phenotype, as discussed previously. Therefore, treatment of nosocomial infections caused by *A. baumannii* has become complicated because of the widespread antimicrobial resistance among these organisms<sup>[36]</sup>. The rising trend of resistance in *A. baumannii* strains, particularly to newer antimicrobial agents, is a health care concern. The organism expresses multiple mechanisms of antibiotic resistance that likely leads to the development of multiply resistant or even “pan-resistant” strains. This situation is particularly a quandary in terms of therapeutic choices for epidemic outbreaks mediated by these phenotypes.

## POTENTIAL SOURCES OF INFECTION AND CONTAMINATION

The source of *A. baumannii* infections can be endogenous or exogenous. Most frequently, the infection is exogenous in origin because of the ability of the organisms to survive longer in the environment and on dry surfaces and because they are resistant to desiccation. *A. baumannii* multiply not only on human and animal skin, but also in soil and water and thus have a diversity of reservoirs. Locations in the hospital environment where *A. baumannii* have been found include ventilator tubing, suction catheters, humidifiers, containers of distilled water, urine collection jugs, intravenous nutrition, multidose vials of medication, potable water, moist bedding articles, pillows, and inadequately sterilized reusable arterial pressure transducers<sup>[37-39]</sup>. *A. baumannii* have been found in or on water taps, sinks, and computer keyboards and on all other inanimate surfaces that can act as a reservoir<sup>[40,41]</sup>. Hospital food can also be a potential source of *Acinetobacter* infection<sup>[8]</sup>. A study of two hospital outbreaks in Leiden, the Netherlands, reported the isolation of the outbreak strains from the dust inside the respiratory ventilator, the apparatus used to cool or warm a patient<sup>[40]</sup>.

The gloves, gowns, and unwashed hands of hospital staff including doctors and nurses are frequently contaminated and may act as a potential source of *Acinetobacter* infection<sup>[14,42]</sup>. Hospital staffs with damaged skin are at increased risk of being colonized with *Acinetobacter* and are more likely to contaminate medical equipment and devices and patients by direct contact, thereby causing outbreaks of infection<sup>[43]</sup>. Specific types of medical procedures are also reportedly associated with high rates of infection with *Acinetobacter*, such as wound irrigation and treatment, catheterization, and tracheostomy<sup>[44]</sup>. Thus, the mode of infection can be environmental contamination or cross-contamination<sup>[45]</sup>. Community-acquired *A. baumannii* pneumonia is one of the severe forms of infection found around Indian Ocean, with very high co-morbidities and



reportedly associated in part with casualties from natural disasters such as earthquake and tsunamis, and wound contamination occurring among soldiers following war-related injuries<sup>[46]</sup>.

## NOSOCOMIAL ACQUISITION AND RISK FACTORS

Several factors reported by different groups increase the risk of nosocomial infection with *A. baumannii*. Most vulnerable among them are mechanical ventilation (source of ventilator-associated pneumonia), intensive care and other critical care units, wound and burn units, prolonged hospital stay, prior antibiotic therapy, increased exposures to infected patients, colonized neighboring patients, and health care personnel. Other risk factors are a weakened immune system, chronic and debilitating disease, and diabetes. Infection secondary to an invasive procedure is widely reported and involves ventilator-associated pneumonia, secondary meningitis and bloodstream infection, urinary tract infection, surgical site infection, and catheter-related bloodstream infection. In most cases it is point source contamination. Postoperative complications from infection with *A. baumannii* have been reported; the major risk factors are skin and soft tissue, bone, central nervous system trauma or injuries, and combat wounds and injuries<sup>[47-49]</sup>. Post-disaster infections caused by *A. baumannii* have also been reported<sup>[50,51]</sup>. *A. baumannii* is intrinsically resistant to many antimicrobial agents and has a propensity to acquire resistance to other, newer antimicrobial agents as well<sup>[52]</sup>. Consequently, it has become more prevalent because of selective pressure from antimicrobial agents in ICUs. Analysis of the epidemiological profile of antibiotic-resistant *Acinetobacter* spp showed an increased risk of infection in patients in ICUs who probably spread large numbers of *A. baumannii* cells into their surroundings by shedding *A. baumannii*-infected or colonized cells, making the area more likely to be a source of infection for others<sup>[37,53]</sup>. Although airborne transmission has been documented, direct contact, including patient-to-patient and health care-provider-to-patient transmission, is more relevant.

Community acquisition of *Acinetobacter* infection, although rare, has been reported<sup>[54,55]</sup>, and a community-acquired MDR *Acinetobacter* carrying IMP1 metallo- $\beta$ -lactamase, responsible for hospital infection, is recovered<sup>[55]</sup>. Community-acquired *A. baumannii* pneumonia<sup>[56,57]</sup>, community-acquired bacteremia<sup>[58]</sup>, urinary tract infection<sup>[59]</sup>, and meningitis<sup>[54]</sup> have been reported. On the basis of the rising incidence of community-acquired *A. baumannii* infection, a concurrent spread of multidrug resistance is the greatest risk. Among, *A. baumannii* wound infections, three hypotheses usually described are a combination of wound with environmental bacteria, a wound contamination from previous cutaneous or oropharyngeal endogenous reservoir, and hospital acquisition<sup>[46]</sup>.

## STRATEGIES TO CONTROL INFECTION

Outbreaks, particularly endemic or periodic epidemic outbreaks, caused by MDR *A. baumannii* are difficult to control. It is still possible to effectively control *A. baumannii*, although eradication is in question<sup>[14]</sup>. Decontamination of the patient by treating the gut and skin has been reported. Antibiotics can be used to inhibit gut colonization by *A. baumannii* that remains susceptible, but the benefits are limited because of the risk of developing resistant phenotypes. Additional research is needed to clarify the role of such techniques for selective decontamination of gut compared with surfaces such as skin<sup>[60]</sup>. The role of various sites of *A. baumannii* colonization and the risk of epidemiological outbreaks have been assessed; selective gut decontamination was found to be less effective as an additional measure<sup>[61]</sup>. Selective decontamination of skin with chlorhexidine reduced a significant load of *A. baumannii* and has been proposed as the infection control measure to lower the number of endemic outbreaks<sup>[62]</sup>. Because *A. baumannii* is widely present in the hospital environment, it can contaminate any surface or article with which it comes in contact, *e.g.*, resuscitation bags, blood pressure cuffs, parenteral fluids and nutritional solutions, lotion dispensers, hand creams, bed linen, and mattresses. Therefore strict hand hygiene and personal cleanliness are essential in breaking the route of transmission<sup>[63]</sup>. Periodic disinfection of wards, units, and surfaces and sterilization of medical devices using appropriate methods are highly recommended. A periodic hospital environmental sample survey for microbiological contamination is advisable<sup>[64,65]</sup>. The epidemiological studies help to identify the source or reservoir of the infection and thus eventually to understand how to control the outbreaks<sup>[8]</sup>. Control of the environmental reservoir is a major part of an effective control strategy<sup>[64,66]</sup>. The researchers who conducted the study in the Netherlands controlled an outbreak by removing dust from the mechanical ventilator and continuous venovenous hemofiltration machines and replacing dust filters<sup>[40]</sup>. A study conducted in the United States reported *A. baumannii* as a model in eradication of MDR infections<sup>[67]</sup>. The control measures for *A. baumannii* infection have been discussed by many investigators<sup>[8,18,68,69]</sup>. Some of the specific control measures for *A. baumannii* infection are shown in Table 1.

One of the most associated factors with reservoirs is biofilm formation capability of *A. baumannii* wherein it is responsible in part for the intermittent release of pathogens that leads to outbreaks. Biofilm formation by this organism also facilitates its persistence, and thus acts as a source of infection<sup>[25]</sup>. Recently, a dynamic exchange of gene cassettes between integrons (a mobile genetic element responsible for recruitment of multiple resistance genes, *e.g.*, class 1 integron) in natural biofilms has been demonstrated<sup>[25,79]</sup>. This association of biofilm is important in higher tolerance or resistance to strong

**Table 1** Some of the major infection control measures marked for *Acinetobacter baumannii* infection outbreaks

Sr	Effective control measure	Ref
1	Early detection of a colonized patient or the source or reservoir of an infection	[14,70]
2	Eradication of the source or reservoir	[71]
3	Isolation of an infected or colonized patient into an isolation cubicle	[18]
4	Cohort nursing	[72]
5	Emphasis on hand washing (with alcoholic-based disinfectants) before and after patient handling	[73]
6	Use of disposable gloves and aprons	[42]
7	Prohibition of sale of antibiotics without prescription/judicious use of antibiotics	[69,74]
8	Improved surveillance system for antimicrobial resistance	[75]
9	Adherence to infection control best practices	[76]
10	Education of hospital staff and community for infection control/proper drug use and maintenance of hygiene/contact precaution	[77,78]

antimicrobial and biocidal agent<sup>[80]</sup>. Biofilm producing virulence is also found associated with aminoglycoside resistance genes. Rajamohan *et al.*<sup>[25]</sup> demonstrated an increased biocide resistance and multidrug resistance in *A. baumannii* associated with the ability to form stronger biofilms. In part, the resistance may be increasing due to low penetration of antimicrobials into biofilms, in addition to acquisition of resistance genes through mobile genetic elements<sup>[81]</sup>. The continuous presence of high selection pressure of antimicrobials and disinfectants in intensive care units is also been correlated to increased multidrug resistance, strong biofilm abilities, and survival of these variant within such biofilms<sup>[16,82]</sup>. Thus control of such variants are a challenge, and difficult with routine antimicrobial and biocidal agents.

Microbiology laboratories can provide frontline surveillance for antibiotic resistance and are therefore useful in combating nosocomial infections<sup>[83]</sup>. Rapid, accurate analysis of antimicrobial susceptibility will be useful in determining the precise use of antimicrobial agents. Hence, clinical input from a microbiologist is necessary to keep one step ahead in controlling nosocomial infections. Periodic surveillance by molecular typing of isolates from patients is recommended for early detection of an epidemic strain, which consequently serves as an effective control measure<sup>[84]</sup>. Empiric antimicrobial therapy based on such observations is useful when laboratory findings are impeded for one reason or another<sup>[85,86]</sup>. Such therapy has been successful against pneumonias, ventilator-associated pneumonias, and bloodstream infections caused by *A. baumannii*, especially in critically ill patients<sup>[87-90]</sup>, although some failures have also been reported, and caution is advised<sup>[91]</sup>. Empiric carbapenem therapy is a popular example of such a regime<sup>[14,92,93]</sup>. With the rise of carbapenem resistance in MDR phenotypes, this approach seemingly faces difficulties<sup>[14]</sup>. MDR is a common phenomenon associated with *A. baumannii* that is on the increase<sup>[10,94-96]</sup>. There are no clear guidelines to treat *A. baumannii* infections,

and antipseudomonal broad-spectrum penicillins and cephalosporins and the members of other categories such as monobactams, aminoglycosides, fluoroquinolones, carbapenems, glycolcyclines, polymyxins, and  $\beta$ -lactamase inhibitors are used to control infections involving *A. baumannii*. Selection of the appropriate antimicrobial agent for empirical therapy is therefore challenging and has to be based on local institutional and hospital findings. Treatment decisions are usually made on a case-by-case basis by a health care provider. Empirical treatment therefore is likely to differ for a given geographic location<sup>[97]</sup>. Antibiotic susceptibility testing and other phenotypic tests for detecting double-disk synergy should be used as a guide, in addition to approved governing guidelines. Institutional data mining and retrospective analysis are often of great help in this regard and are advised by Towner<sup>[10]</sup>.

Because of the limited choice of antimicrobial agents, *A. baumannii* infections are treated mainly with extended-spectrum  $\beta$ -lactams;  $\beta$ -lactams with  $\beta$ -lactamase inhibitors such as tazobactam or sulbactam; and carbapenems. Colistin and sulbactam are still relatively effective against infection caused by MDR *A. baumannii*, but an anticipatory fear of the development of resistance is increasing in ICUs. Peptides and other novel antibacterial agents are in the experimental phases. A combination therapy (dual or triple therapy) of a carbapenem with sulbactam, tobramycin, colistin, and aztreonam is being assessed in laboratory synergy studies, but clinical trials are required before one can adopt such combination regimens<sup>[98]</sup>. A study containing pharmacokinetic-pharmacodynamic profiling of four antimicrobial drugs against *A. baumannii* suggested that a combination involving carbapenem is required for effective therapy<sup>[99]</sup>. A glycopeptide (vancomycin or teicoplanin)-colistin combination was found to be highly active (synergism) against *A. baumannii* both *in vitro* and in a simple animal model<sup>[100]</sup>. A complicated case of persistent MDR *A. baumannii* central nervous system infection (ventriculitis) was resolved by a prolonged triple combination therapy involving intraventricular colistin and tobramycin plus intravenous colistin, rifampin, and vancomycin<sup>[101]</sup>. In murine pneumonia and rabbit meningitis models of *A. baumannii* infection, imipenem or sulbactam were found to be appropriate for combination therapy when used with rifampin<sup>[102]</sup>. A comparative *in vitro* study of synergistic activities also demonstrated that imipenem has better synergism with colistin than does amikacin or ampicillin/sulbactam against carbapenem-resistant *A. baumannii*<sup>[103]</sup>. In another study, tigecycline, a recently developed novel broad-spectrum antibacterial agent, was used (off-label indication) in combination therapy to treat MDR *A. baumannii* superinfection. However, the studies had several limitations such as retrospective design, small number of patients, and tigecycline as a part of the combination<sup>[56]</sup>. Despite its association with nephrotoxicity, colistin has been used by different modes of administration. Nebulized colistin was found to be more efficient in *A. baumannii* pulmonary infections when administered solely in nebulized

**Table 2** Some of the commonly reported mechanisms of resistance in *Acinetobacter baumannii* from different geographic locations

Category of mechanism	Gene involved	Geo-location	Ref
ESBL	PER-1 type	Hungary, India, Turkey, Korea, France, Belgium, Romania	[114,127-132]
ESBL	VEB-1 type	Belgium, France	[131,133]
ESBL	KPC type		[134]
ESBL	CTX-M-2 type	Japan	[135]
Carbapenemase	OXA type	United Kingdom, transcontinental	[120,136]
Carbapenemase	OXA type	United States,	[119,122,123,137]
Carbapenemase	OXA-51 type	United Kingdom, France, Iraq, United States	[123,138-140]
Carbapenemase	OXA-23 type	United Kingdom, China, United States	[141,142]
Carbapenemase	OXA-40 type	Spain, United States	[123,143]
Carbapenemase	OXA-58 type	Greece, Italy, Bolivia	[144,145]
Carbapenemase (multiple)	OXA, IMP, VIM	Korea	[146]
Carbapenemase, MBL	NDM	Israel, Germany	[147,148]
Carbapenemase, MBL	VIM	Poland	[149]
Carbapenemase, MBL	IMP	Japan, Brazil	[150,151]
Carbapenemase, MBL	SIM	China	[152]

ESBL: Extended-spectrum  $\beta$ -lactamase; MBL: Metallo- $\beta$ -lactamase

form or in combination with intravenous colistin against intravenous colistin alone<sup>[104]</sup>. Colistin is still considered a good choice against MDR *A. baumannii* compared with ampicillin/sulbactam<sup>[105-107]</sup> or rifampin+imipenem<sup>[107]</sup>. The nephrotoxicity associated with colistin is reported to be reversible and less frequent than once thought. Neurotoxicity is rare, although more posological research is needed<sup>[133]</sup>. At present, no new drugs that could be available in 5 years are currently in the pipeline; therefore, combination regimens of antibiotics are the only resources to combat this infection.

## ANTIMICROBIAL RESISTANCE IN *A. BAUMANNII*

The three major forces that drive antimicrobial drug resistance are failure to maintain hospital hygiene, selective pressure due to irrational use of antibiotics, and mobile genetic elements encoding the bacterial resistance mechanism<sup>[96]</sup>. The resistance among *A. baumannii* strains to  $\beta$ -lactam agents is of great concern among clinicians. The  $\beta$ -lactams are broadly accepted for treatment because of the availability of a wide range of drugs, their broad spectrum of activity, minimum side effects, and most importantly, their relatively low cost in developing countries of Africa, Asia and Latin America. The restriction on the use of these agents because of the emergence of resistance is a loss to the community and a great blow to the health care system. The mechanism of resistance to  $\beta$ -lactam in *A. baumannii* can be attributed to an intrinsic property or an acquired phenomenon. This organism is a known reservoir of multiple plasmids carrying antibiotic resistance markers<sup>[16,95]</sup>. The later mobile genetic element is of concern because the acquisition of resistance genes can radically change the scenario of drug resistance. *Acinetobacter* spp are also known to donate resistance-plasmids and are therefore likely to rapidly disseminate resistance among other commensals

or pathogens.

*Acinetobacter* harbors multiple mechanisms of drug resistance. The mechanism of resistance to  $\beta$ -lactam agents in *A. baumannii* involves production of a variety of chromosomal or plasmid-mediated  $\beta$ -lactamases, especially extended-spectrum  $\beta$ -lactamase (ESBL), alteration of drug-binding proteins, permeability changes in the cell membrane, loss of porins, and efflux pump, of which the presence of an array of  $\beta$ -lactamases is the predominant weapon<sup>[108-111]</sup>. *Acinetobacter* produce a variety of  $\beta$ -lactamases. The main mechanisms of resistance to extended-spectrum cephalosporins in *A. baumannii* are the over-expression of chromosomal cephalosporinases and plasmid-encoded Ambler class A, B, and D  $\beta$ -lactamases<sup>[112]</sup>. ESBL-producing *A. baumannii* strains are now reported from various geographic areas of the world. These include the TEM type, SHV type, CTX-M type, PER-1, and VEB-1  $\beta$ -lactamases. The prevalence of ESBLs is much higher in the isolates from ICUs than in isolates from other hospital sites<sup>[113,114]</sup>. *A. baumannii* produces a variety of extended-spectrum  $\beta$ -lactamases, depending on its geographical location. The PER-1 ESBLs were from Turkey, Korea, Russia, Romania, Belgium, France, and India; VEB-1, from France and Belgium; TEM-116 and TEM-92, from China and Italy, respectively; SHV-12 from the Netherlands; CTX-M-2 and CTX-M-43 from Korea and Bolivia (Italy), respectively<sup>[114-118]</sup>. Table 2 demonstrates in brief the representative mechanisms reported from different geographic locations. It was believed that ESBL-producing *A. baumannii* strains remain susceptible to carbapenems. However, OXA-type ESBL-producing *A. baumannii* isolates resistant to carbapenems have been widely reported, including from the United States<sup>[119-122]</sup>, that carry insertion sequence, IS<sub>Aba1</sub> upstream to OXA-like genes<sup>[123]</sup>. Although resistance in *A. baumannii* to polymyxins such as colistin is rare, recent reports suggest that an underlying mechanism of moderate resistance to colistin involves point mutation in pmrB, upregulation of pm-



rAB, and expression of pmrC, which lead to phosphoethanolamine modification of lipid A<sup>[33,124]</sup>. This finding means that we will not be able to use many more  $\beta$ -lactam drugs, which will further limit our options. Among carbapenem-resistant MDR *A. baumannii*, colistin is often the last resort. Recent findings suggest a slow rise of colistin-resistant isolates lead to Pan-drug resistant organisms<sup>[125]</sup>. With the help of rapid and powerful tools such as high throughput sequencing technologies e.g., whole-genome sequencing, one can elucidate the origin of large outbreaks of such resistant pathogens, and the exact genetics behind resistance mechanisms<sup>[125,126]</sup>.

## FUTURE PROBLEMS

A contentment of multidrug resistance and their dissemination in *Acinetobacter baumannii* is not an easy task. While multiple drug resistance is increasing in this pathogen, and carbapenem resistance is rapidly spreading cross-continently, there is a sharp decline in development of new antimicrobial agents that can control MDR *A. baumannii*. There is no new drug in pharmaceutical pipeline or none of the FDA-approved antimicrobial compounds tested had appreciable effect in control of MDR *A. baumannii*. The existing antimicrobials also failed to control the resistance development and effective elimination of MDR variants. A rational synergistic approach of some of the combination therapies although working, needs more in-depth understanding, and systematic studies are required in order to control probably outbreaks. Creation of pan-drug resistant variants will have to be avoided, and efforts on new anti-acinetobacter drug development would be invested.

## CONCLUSION

Microbiological surveillance facilitates the ability to monitor changes in the trends of dominant microorganisms and their antimicrobial susceptibilities in hospitals. It helps to detect recent resistance mechanisms in these pathogens and to formulate antimicrobial usage policies for the hospital and adds to the epidemiological information about these organisms in particular regions of the country.

The MDR *Acinetobacter* clinical isolates, especially in the ICUs of hospitals, are a serious public health concern worldwide, and responsible for high mortality. The geographic variation in resistance patterns emphasizes the importance of local surveillance in determining the most suitable therapeutic option to treat *Acinetobacter* infections. The lack of therapeutic options for treating MDR organisms calls for systematic pharmacokinetic and pharmacodynamic studies of rational combination therapies until new, powerful drug appear in clinical practice for this purpose.

## ACKNOWLEDGMENTS

Authors thank Pamela Fried of Drexel University College of Medicine Academic Publishing Services for editorial help with the manuscript.

## REFERENCES

- 1 **Slama TG.** Gram-negative antibiotic resistance: there is a price to pay. *Crit Care* 2008; **12** Suppl 4: S4 [PMID: 18495061 DOI: 10.1186/cc6820]
- 2 **Gaynes R, Edwards JR.** Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 2005; **41**: 848-854 [PMID: 16107985 DOI: 10.1086/432803]
- 3 **Gales AC, Jones RN, Forward KR, Liñares J, Sader HS, Verhoef J.** Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). *Clin Infect Dis* 2001; **32** Suppl 2: S104-S113 [PMID: 11320451 DOI: 10.1086/320183]
- 4 **Rossau R, van Landschoot A, Gillis M, De Ley J.** Taxonomy of Moraxellaceae fam. nov., a New Bacterial Family To Accommodate the Genera Moraxella, Acinetobacter, and Psychrobacter and Related Organisms. *Int J Syst Bacteriol* 1991; **41**: 310-319 [DOI: 10.1099/00207713-41-2-310]
- 5 **Juni E.** Interspecies transformation of *Acinetobacter*: genetic evidence for a ubiquitous genus. *J Bacteriol* 1972; **112**: 917-931 [PMID: 4563985]
- 6 **Doi Y, Onuoha EO, Adams-Haduch JM, Pakstis DL, McGaha TL, Werner CA, Parker BN, Brooks MM, Shutt KA, Pasculle AW, Muto CA, Harrison LH.** Screening for *Acinetobacter baumannii* colonization by use of sponges. *J Clin Microbiol* 2011; **49**: 154-158 [PMID: 20980559 DOI: 10.1128/JCM.01043-10]
- 7 **Bauvet P, Grimont P.** Taxonomy of the genus *Acinetobacter* with the recognition of *Acinetobacter baumannii* sp. nov., *Acinetobacter haemolyticus* sp. nov., *Acinetobacter johnsonii* sp. nov., and *Acinetobacter junii* sp. nov., and emended descriptions of *Acinetobacter calcoaceticus* and *Acinetobacter lwoffii*. *Int J Syst Bacteriol* 1986; **36**: 228-240 [DOI: 10.1099/00207713-36-2-228]
- 8 **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]
- 9 **Tjernberg I, Ursing J.** Clinical strains of *Acinetobacter* classified by DNA-DNA hybridization. *APMIS* 1989; **97**: 595-605 [PMID: 2751895 DOI: 10.1111/j.1699-0463.1989.tb00449.x]
- 10 **Towner KJ.** *Acinetobacter*: an old friend, but a new enemy. *J Hosp Infect* 2009; **73**: 355-363 [PMID: 19700220 DOI: 10.1016/j.jhin.2009.03.032]
- 11 **Zarrilli R, Pournaras S, Giannouli M, Tsakris A.** Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. *Int J Antimicrob Agents* 2013; **41**: 11-19 [PMID: 23127486 DOI: 10.1016/j.ijantimicag.2012.09.008]
- 12 **Zarrilli R, Di Popolo A, Bagattini M, Giannouli M, Martino D, Barchitta M, Quattrocchi A, Iula VD, de Luca C, Scarcella A, Triassi M, Agodi A.** Clonal spread and patient risk factors for acquisition of extensively drug-resistant *Acinetobacter baumannii* in a neonatal intensive care unit in Italy. *J Hosp Infect* 2012; **82**: 260-265 [PMID: 23102814 DOI: 10.1016/j.jhin.2012.08.018]
- 13 **Sarovich DS, Colman RE, Price EP, Massire C, Von Schulze AT, Waddell V, Anderson SM, Ecker DJ, Liguori AP, Engelthaler DM, Sampath R, Keim P, Eshoo MW, Wagner DM.** Molecular Genotyping of *Acinetobacter* spp. Isolated in Arizona, United States, using Multilocus PCR and Mass Spectrometry. *J Med Microbiol* 2013 Jun 5; [Epub ahead of print] [PMID: 23741021 DOI: 10.1099/jmm.0.052381-0]
- 14 **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]
- 15 **Giannouli M, Cuccurullo S, Crivaro V, Di Popolo A, Ber-**

- nardo M, Tomasone F, Amato G, Brisse S, Triassi M, Utili R, Zarrilli R. Molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* in a tertiary care hospital in Naples, Italy, shows the emergence of a novel epidemic clone. *J Clin Microbiol* 2010; **48**: 1223-1230 [PMID: 20181918 DOI: 10.1128/JCM.02263-09]
- 16 **Bergogne-Bérézin E**, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. *Clin Microbiol Rev* 1996; **9**: 148-165 [PMID: 8964033]
- 17 **Bouvet PJ**, Grimont PA. Identification and biotyping of clinical isolates of *Acinetobacter*. *Ann Inst Pasteur Microbiol* 1987; **138**: 569-578 [PMID: 3440090 DOI: 10.1016/0769-2609(87)90042-1]
- 18 **Crowe M**, Towner KJ, Humphreys H. Clinical and epidemiological features of an outbreak of *acinetobacter* infection in an intensive therapy unit. *J Med Microbiol* 1995; **43**: 55-62 [PMID: 7608957 DOI: 10.1099/00222615-43-1-55]
- 19 **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]
- 20 **Diancourt L**, Passet V, Nemec A, Dijkshoorn L, Brisse S. The population structure of *Acinetobacter baumannii*: expanding multiresistant clones from an ancestral susceptible genetic pool. *PLoS One* 2010; **5**: e10034 [PMID: 20383326 DOI: 10.1371/journal.pone.0010034]
- 21 **Thom KA**, Hsiao WW, Harris AD, Stine OC, Rasko DA, Johnson JK. Patients with *Acinetobacter baumannii* bloodstream infections are colonized in the gastrointestinal tract with identical strains. *Am J Infect Control* 2010; **38**: 751-753 [PMID: 20570393 DOI: 10.1016/j.ajic.2010.03.005]
- 22 **Gerner-Smidt P**. Ribotyping of the *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex. *J Clin Microbiol* 1992; **30**: 2680-2685 [PMID: 1383266]
- 23 **Gouby A**, Carles-Nurit MJ, Bouziges N, Bourg G, Mesnard R, Bouvet PJ. Use of pulsed-field gel electrophoresis for investigation of hospital outbreaks of *Acinetobacter baumannii*. *J Clin Microbiol* 1992; **30**: 1588-1591 [PMID: 1352519]
- 24 **Seifert H**, Baginski R, Schulze A, Pulverer G. Antimicrobial susceptibility of *Acinetobacter* species. *Antimicrob Agents Chemother* 1993; **37**: 750-753 [PMID: 8494371 DOI: 10.1128/AAC.37.4.750]
- 25 **Rajamohan G**, Srinivasan VB, Gebreyes WA. Biocide-tolerant multidrug-resistant *Acinetobacter baumannii* clinical strains are associated with higher biofilm formation. *J Hosp Infect* 2009; **73**: 287-289 [PMID: 19762119]
- 26 **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]
- 27 **Antunes LC**, Imperi F, Towner KJ, Visca P. Genome-assisted identification of putative iron-utilization genes in *Acinetobacter baumannii* and their distribution among a genotypically diverse collection of clinical isolates. *Res Microbiol* 2011; **162**: 279-284 [PMID: 21144895 DOI: 10.1016/j.resmic.2010.10.010]
- 28 **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, Cruveillé S. Comparative analysis of *Acinetobacter* genomes for three lifestyles. *PLoS One* 2008; **3**: e1805 [PMID: 18350144 DOI: 10.1371/journal.pone.0001805]
- 29 **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]
- 30 **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]
- 31 **Cerqueira GM**, Peleg AY. Insights into *Acinetobacter baumannii* pathogenicity. *IUBMB Life* 2011; **63**: 1055-1060 [PMID: 21989983 DOI: 10.1002/iub.533]
- 32 **Karageorgopoulos DE**, Falagas ME. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. *Lancet Infect Dis* 2008; **8**: 751-762 [PMID: 19022191 DOI: 10.1016/S1473-3099(08)70279-2]
- 33 **Lim LM**, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A, Forrest A, Bulitta JB, Tsuji BT. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. *Pharmacotherapy* 2010; **30**: 1279-1291 [PMID: 21114395 DOI: 10.1592/phco.30.12.1279]
- 34 **Coelho JM**, Turton JF, Kaufmann ME, Glover J, Woodford N, Warner M, Palepou MF, Pike R, Pitt TL, Patel BC, Livermore DM. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. *J Clin Microbiol* 2006; **44**: 3623-3627 [PMID: 17021090 DOI: 10.1128/JCM.00699-06]
- 35 **Spence RP**, Towner KJ, Henwood CJ, James D, Woodford N, Livermore DM. Population structure and antibiotic resistance of *Acinetobacter* DNA group 2 and 13TU isolates from hospitals in the UK. *J Med Microbiol* 2002; **51**: 1107-1112 [PMID: 12466410]
- 36 **Seifert H**, Boullion B, Schulze A, Pulverer G. Plasmid DNA profiles of *Acinetobacter baumannii*: clinical application in a complex endemic setting. *Infect Control Hosp Epidemiol* 1994; **15**: 520-528 [PMID: 7983345]
- 37 **Paterson DL**. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis* 2006; **43** Suppl 2: S43-48 [DOI: 10.1086/504476]
- 38 **Villegas MV**, Hartstein AI. *Acinetobacter* outbreaks, 1977-2000. *Infect Control Hosp Epidemiol* 2003; **24**: 284-295 [PMID: 12725359 DOI: 10.1086/502205]
- 39 **Weernink A**, Severin WP, Tjernberg I, Dijkshoorn L. Pillows, an unexpected source of *Acinetobacter*. *J Hosp Infect* 1995; **29**: 189-199 [PMID: 7615936]
- 40 **Bernards AT**, Harinck HI, Dijkshoorn L, van der Reijden TJ, van den Broek PJ. Persistent *Acinetobacter baumannii*? Look inside your medical equipment. *Infect Control Hosp Epidemiol* 2004; **25**: 1002-1004 [PMID: 15566039 DOI: 10.1086/502335]
- 41 **Neely AN**, Maley MP, Warden GD. Computer keyboards as reservoirs for *Acinetobacter baumannii* in a burn hospital. *Clin Infect Dis* 1999; **29**: 1358-1360 [PMID: 10525257 DOI: 10.1086/313463]
- 42 **Morgan DJ**, Liang SY, Smith CL, Johnson JK, Harris AD, Furuno JP, Thom KA, Snyder GM, Day HR, Perencevich EN. Frequent multidrug-resistant *Acinetobacter baumannii* contamination of gloves, gowns, and hands of healthcare workers. *Infect Control Hosp Epidemiol* 2010; **31**: 716-721 [PMID: 20486855 DOI: 10.1086/653201]
- 43 **Bayuga S**, Zeana C, Sahni J, Della-Latta P, el-Sadr W, Larson E. Prevalence and antimicrobial patterns of *Acinetobacter baumannii* on hands and nares of hospital personnel and patients: the iceberg phenomenon again. *Heart Lung* 2002; **31**: 382-390 [PMID: 12487017]
- 44 **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]
- 45 **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]
- 46 **Eveillard M**, Joly-Guillou ML. [Emerging *Acinetobacter baumannii* infections and factors favouring their occurrence]. *Pathol Biol* (Paris) 2012; **60**: 314-319 [PMID: 21963271 DOI: 10.1016/j.patbio.2011.08.002]
  - 47 **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, Petruccielli 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]
  - 48 **Scott PT**, Petersen K, Fishbain J, Craft DW, Ewell AJ, Moran K, Hack DC, Deye GA, Riddell S, Christopher G, Mancuso JD, Petruccielli BP, Endy T, Lindler L, Davis K, Milstrey EG, Brosch L, Pool J, Blankenship CL, Witt CJ, Malone JL, Tornberg DN, Srinivasan A. *Acinetobacter baumannii* Infections Among Patients at Military Medical Facilities Treating Injured U.S Service Members, 2002-2004. *MMWR* 2004; **53**: 1063-1066
  - 49 **Sebeny PJ**, Riddle MS, Petersen K. *Acinetobacter baumannii* skin and soft-tissue infection associated with war trauma. *Clin Infect Dis* 2008; **47**: 444-449 [PMID: 18611157 DOI: 10.1086/590568]
  - 50 **Maegle M**, Gregor S, Steinhausen E, Bouillon B, Heiss MM, Perbix W, Wappler F, Rixen D, Geisen J, Berger-Schreck B, Schwarz R. The long-distance tertiary air transfer and care of tsunami victims: injury pattern and microbiological and psychological aspects. *Crit Care Med* 2005; **33**: 1136-1140 [PMID: 15891349]
  - 51 **Oncül O**, Keskin O, Acar HV, Küçükardali Y, Evrenkaya R, Atasoy EM, Top C, Nalbant S, Ozkan S, Emekdaş G, Cavuşlu S, Us MH, Pahsa A, Gökben M. Hospital-acquired infections following the 1999 Marmara earthquake. *J Hosp Infect* 2002; **51**: 47-51 [PMID: 12009820 DOI: 10.1053/jhin.2002.1205]
  - 52 **Abbo A**, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, Carmeli Y. Multidrug-resistant *Acinetobacter baumannii*. *Emerg Infect Dis* 2005; **11**: 22-29 [PMID: 15705318 DOI: 10.3201/eid1101.040001]
  - 53 **Paterson DL**. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis* 2006; **43** Suppl 2: S43-S48 [PMID: 16894514]
  - 54 **Ozaki T**, Nishimura N, Arakawa Y, Suzuki M, Narita A, Yamamoto Y, Koyama N, Nakane K, Yasuda N, Funahashi K. Community-acquired *Acinetobacter baumannii* meningitis in a previously healthy 14-month-old boy. *J Infect Chemother* 2009; **15**: 322-324 [PMID: 19856071 DOI: 10.1007/s10156-009-0704-x]
  - 55 **Telang NV**, Satpute MG, Dhakephalkar PK, Niphadkar KB, Joshi SG. Fulminating septicemia due to persistent pan-resistant community-acquired metallo- $\beta$ -lactamase (IMP-1)-positive *Acinetobacter baumannii*. *Indian J Pathol Microbiol* 2011; **54**: 180-182 [PMID: 21393912 DOI: 10.4103/0377-4929.77397]
  - 56 **Guner R**, Hasanoglu I, Keske S, Kalem AK, Tasyaran MA. Outcomes in patients infected with carbapenem-resistant *Acinetobacter baumannii* and treated with tigecycline alone or in combination therapy. *Infection* 2011; **39**: 515-518 [PMID: 21789524 DOI: 10.1007/s15010-011-0161-1]
  - 57 **Moreira Silva G**, Morais L, Marques L, Senra V. *Acinetobacter* community-acquired pneumonia in a healthy child. *Rev Port Pneumol* 2012; **18**: 96-98 [PMID: 21963110 DOI: 10.1016/j.rppneu.2011.07.006]
  - 58 **Obaro S**, Lawson L, Essen U, Ibrahim K, Brooks K, Otuneye A, Shetima D, Ahmed P, Ajose T, Olugbile M, Idiong D, Ogundeji D, Ochigbo C, Olanipekun G, Khalife W, Adegbola R. Community acquired bacteremia in young children from central Nigeria--a pilot study. *BMC Infect Dis* 2011; **11**: 137 [PMID: 21595963 DOI: 10.1186/1471-2334-11-137]
  - 59 **Solak Y**, Atalay H, Turkmen K, Biyik Z, Genc N, Yeksan M. Community-acquired carbapenem-resistant *Acinetobacter baumannii* urinary tract infection just after marriage in a renal transplant recipient. *Transpl Infect Dis* 2011; **13**: 638-640 [PMID: 21504527 DOI: 10.1111/j.1399-3062.2011.00637.x]
  - 60 **Donskey CJ**. Antibiotic regimens and intestinal colonization with antibiotic-resistant gram-negative bacilli. *Clin Infect Dis* 2006; **43** Suppl 2: S62-S69 [PMID: 16894517 DOI: 10.1086/504481]
  - 61 **Ayats J**, Corbella X, Ardanuy C, Domínguez MA, Ricart A, Ariza J, Martin R, Liñares J. Epidemiological significance of cutaneous, pharyngeal, and digestive tract colonization by multiresistant *Acinetobacter baumannii* in ICU patients. *J Hosp Infect* 1997; **37**: 287-295 [PMID: 9457606]
  - 62 **Borer A**, Gilad J, Porat N, Megrelesvilli R, Saidel-Odes L, Peled N, Eskira S, Schlaeffer F, Almog Y. Impact of 4% chlorhexidine whole-body washing on multidrug-resistant *Acinetobacter baumannii* skin colonisation among patients in a medical intensive care unit. *J Hosp Infect* 2007; **67**: 149-155 [PMID: 17900759 DOI: 10.1016/j.jhin.2007.07.023]
  - 63 **Allegranzi B**, Pittet D. Role of hand hygiene in healthcare-associated infection prevention. *J Hosp Infect* 2009; **73**: 305-315 [PMID: 19720430 DOI: 10.1016/j.jhin.2009.04.019]
  - 64 **Dancer SJ**. The role of environmental cleaning in the control of hospital-acquired infection. *J Hosp Infect* 2009; **73**: 378-385 [PMID: 19726106 DOI: 10.1016/j.jhin.2009.03.030]
  - 65 **Tacconelli E**. Screening and isolation for infection control. *J Hosp Infect* 2009; **73**: 371-377 [PMID: 19699554 DOI: 10.1016/j.jhin.2009.05.002]
  - 66 **Wilks M**, Wilson A, Warwick S, Price E, Kennedy D, Ely A, Millar MR. Control of an outbreak of multidrug-resistant *Acinetobacter baumannii*-calcoaceticus colonization and infection in an intensive care unit (ICU) without closing the ICU or placing patients in isolation. *Infect Control Hosp Epidemiol* 2006; **27**: 654-658 [PMID: 16807837 DOI: 10.1086/507011]
  - 67 **Podnos YD**, Cinat ME, Wilson SE, Cooke J, Gornick W, Thrupp LD. Eradication of multi-drug resistant *Acinetobacter* from an intensive care unit. *Surg Infect* (Larchmt) 2001; **2**: 297-301 [PMID: 12593705 DOI: 10.1089/10962960152813331]
  - 68 **Alp E**, Esel D, Yildiz O, Voss A, Melchers W, Doganay M. Genotypic analysis of *Acinetobacter* bloodstream infection isolates in a Turkish university hospital. *Scand J Infect Dis* 2006; **38**: 335-340 [PMID: 16709534 DOI: 10.1080/00365540500488907]
  - 69 **Sharma R**, Sharma CL, Kapoor B. Antibacterial resistance: current problems and possible solutions. *Indian J Med Sci* 2005; **59**: 120-129 [PMID: 15805685]
  - 70 **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]
  - 71 **Longo B**, Pantosti A, Luzzi I, Tarasi A, Di Sora F, Gallo S, Placanica P, Monaco M, Dionisi AM, Volpe I, Montella F, Cassone A, Rezza G. Molecular findings and antibiotic-resistance in an outbreak of *Acinetobacter baumannii* in an intensive care unit. *Ann Ist Super Sanita* 2007; **43**: 83-88 [PMID: 17536158]
  - 72 **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]
  - 73 **Ayliffe GA**, Babb JR, Davies JG, Lilly HA. Hand disinfection: a comparison of various agents in laboratory and ward

- studies. *J Hosp Infect* 1988; **11**: 226-243 [PMID: 2899107]
- 74 **Harbarth S**, Samore MH. Antimicrobial resistance determinants and future control. *Emerg Infect Dis* 2005; **11**: 794-801 [PMID: 15963271]
- 75 **Dejsirilert S**, Tiengrim S, Sawanpanyalert P, Aswapokee N, Malathum K. Antimicrobial resistance of *Acinetobacter baumannii*: six years of National Antimicrobial Resistance Surveillance Thailand (NARST) surveillance. *J Med Assoc Thai* 2009; **92** Suppl 4: S34-S45 [PMID: 21294501]
- 76 **Miyakis S**, Pefanis A, Tsakris A. The challenges of antimicrobial drug resistance in Greece. *Clin Infect Dis* 2011; **53**: 177-184 [PMID: 21690626 DOI: 10.1093/cid/cir323]
- 77 **Choi WS**, Kim SH, Jeon EG, Son MH, Yoon YK, Kim JY, Kim MJ, Sohn JW, Kim MJ, Park DW. Nosocomial outbreak of carbapenem-resistant *Acinetobacter baumannii* in intensive care units and successful outbreak control program. *J Korean Med Sci* 2010; **25**: 999-1004 [PMID: 20592889 DOI: 10.3346/jkms.2010.25.7.999]
- 78 **Khan MS**, Siddiqui SZ, Haider S, Zafar A, Zafar F, Khan RN, Afshan K, Jabeen A, Khan MS, Hasan R. Infection control education: impact on ventilator-associated pneumonia rates in a public sector intensive care unit in Pakistan. *Trans R Soc Trop Med Hyg* 2009; **103**: 807-811 [PMID: 19342068 DOI: 10.1016/j.trstmh.2009.03.002]
- 79 **Gillings MR**, Holley MP, Stokes HW. Evidence for dynamic exchange of *qac* gene cassettes between class 1 integrons and other integrons in freshwater biofilms. *FEMS Microbiol Lett* 2009; **296**: 282-288 [PMID: 19459951 DOI: 10.1111/j.1574-6968.2009.01646.x]
- 80 **Gaddy JA**, Actis LA. Regulation of *Acinetobacter baumannii* biofilm formation. *Future Microbiol* 2009; **4**: 273-278 [PMID: 19327114 DOI: 10.2217/fmb.09.5]
- 81 **Hoffman LR**, D'Argenio DA, MacCoss MJ, Zhang Z, Jones RA, Miller SI. Aminoglycoside antibiotics induce bacterial biofilm formation. *Nature* 2005; **436**: 1171-1175 [PMID: 16121184 DOI: 10.1038/nature03912]
- 82 **Walsh SE**, Maillard JY, Russell AD, Catrenich CE, Charbonneau DL, Bartolo RG. Development of bacterial resistance to several biocides and effects on antibiotic susceptibility. *J Hosp Infect* 2003; **55**: 98-107 [PMID: 14529633]
- 83 **Hawkey P**. The enemy within: hospital-acquired, antibiotic-resistant bacteria. *Microbiol Today* 2001; **28**: 7-9
- 84 **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 DOI: 10.1089/mdr.2004.10.292]
- 85 **Mathai D**, Lewis MT, Kugler KC, Pfaller MA, Jones RN. Antibacterial activity of 41 antimicrobials tested against over 2773 bacterial isolates from hospitalized patients with pneumonia: I—results from the SENTRY Antimicrobial Surveillance Program (North America, 1998). *Diagn Microbiol Infect Dis* 2001; **39**: 105-116 [PMID: 11248523 DOI: 10.1016/S0732-8893(00)00234-0]
- 86 **Villari P**, Iacuzio L, Torre I, Scarcella A. Molecular epidemiology as an effective tool in the surveillance of infections in the neonatal intensive care unit. *J Infect* 1998; **37**: 274-281 [PMID: 9892532 DOI: 10.1016/S0163-4453(98)92107-7]
- 87 **Rello J**, Paiva JA, Baraibar J, Barcenilla F, Bodi M, Castander D, Correa H, Diaz E, Garnacho J, Llorio M, Rios M, Rodriguez A, Solé-Violán J. International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator-associated Pneumonia. *Chest* 2001; **120**: 955-970 [PMID: 11555535]
- 88 **Munoz-Price LS**, Weinstein RA. *Acinetobacter* infection. *N Engl J Med* 2008; **358**: 1271-1281 [PMID: 18354105 DOI: 10.1056/NEJMra070741]
- 89 **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]
- 90 **Lee NY**, Lee JC, Li MC, Li CW, Ko WC. Empirical antimicrobial therapy for critically ill patients with *Acinetobacter baumannii* bacteremia: Combination is better. *J Microbiol Immunol Infect* 2013 Apr 27; [Epub ahead of print] [PMID: 23632604 DOI: 10.1016/j.jmii.2013.03.004]
- 91 **Micek ST**, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, Hoppe-Bauer J, Dunne WM, Kollef MH. Resistance to empiric antimicrobial treatment predicts outcome in severe sepsis associated with Gram-negative bacteremia. *J Hosp Med* 2011; **6**: 405-410 [PMID: 21916003 DOI: 10.1002/jhm.899]
- 92 **Bradley JS**, Garau J, Lode H, Rolston KV, Wilson SE, Quinn JP. Carbapenems in clinical practice: a guide to their use in serious infection. *Int J Antimicrob Agents* 1999; **11**: 93-100 [PMID: 10221411 DOI: 10.1016/S0924-8579(98)00094-6]
- 93 **Baughman RP**. The use of carbapenems in the treatment of serious infections. *J Intensive Care Med* 2009; **24**: 230-241 [PMID: 19617229 DOI: 10.1177/0885066609335660]
- 94 **Woodford N**, Turton JF, Livermore DM. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011; **35**: 736-755 [PMID: 21303394 DOI: 10.1111/j.1574-6976.2011.00268.x]
- 95 **Joshi SG**, Litake GM, Niphadkar KB, Ghole VS. Multidrug resistant *Acinetobacter baumannii* isolates from a teaching hospital. *J Infect Chemother* 2003; **9**: 187-190 [PMID: 12872781]
- 96 **Weinstein RA**. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerg Infect Dis* 2001; **7**: 188-192 [PMID: 11294703 DOI: 10.3201/eid0702.010206]
- 97 **Felmingham D**. The need for antimicrobial resistance surveillance. *J Antimicrob Chemother* 2002; **50** Suppl S1: 1-7 [PMID: 12239224 DOI: 10.1093/jac/dfk807]
- 98 **Housman ST**, Hagihara M, Nicolau DP, Kuti JL. In vitro pharmacodynamics of human-simulated exposures of ampicillin/sulbactam, doripenem and tigecycline alone and in combination against multidrug-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 2013 May 24; [Epub ahead of print] [PMID: 23710070 DOI: 10.1093/jac/dkt197]
- 99 **Chu YZ**, Tian SF, Chen BY, Nian H, Shang H, Sun GQ. Pharmacokinetic-pharmacodynamic profiling of four antimicrobials against gram-negative bacteria collected from Shenyang, China. *BMC Infect Dis* 2010; **10**: 171 [PMID: 20546625 DOI: 10.1186/1471-2334-10-171]
- 100 **Hornsey M**, Wareham DW. In vivo efficacy of glycopeptide-colistin combination therapies in a *Galleria mellonella* model of *Acinetobacter baumannii* infection. *Antimicrob Agents Chemother* 2011; **55**: 3534-3537 [PMID: 21502628 DOI: 10.1128/AAC.00230-11]
- 101 **Patel JA**, Pacheco SM, Postelnick M, Sutton S. Prolonged triple therapy for persistent multidrug-resistant *Acinetobacter baumannii* ventriculitis. *Am J Health Syst Pharm* 2011; **68**: 1527-1531 [PMID: 21817084 DOI: 10.2146/ajhp100234]
- 102 **Pachón-Ibáñez ME**, Docobo-Pérez F, López-Rojas R, Domínguez-Herrera J, Jiménez-Mejías ME, García-Curiel A, Pichardo C, Jiménez L, Pachón J. Efficacy of rifampin and its combinations with imipenem, sulbactam, and colistin in experimental models of infection caused by imipenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2010; **54**: 1165-1172 [PMID: 20047914 DOI: 10.1128/AAC.00367-09]
- 103 **Sheng WH**, Wang JT, Li SY, Lin YC, Cheng A, Chen YC, Chang SC. Comparative in vitro antimicrobial susceptibilities and synergistic activities of antimicrobial combinations against carbapenem-resistant *Acinetobacter* species: *Acinetobacter baumannii* versus *Acinetobacter genospecies 3* and 13TU. *Diagn Microbiol Infect Dis* 2011; **70**: 380-386 [PMID: 21558048 DOI: 10.1016/j.diagmicrobio.2011.03.003]
- 104 **Pérez-Pedrero MJ**, Sánchez-Casado M, Rodríguez-Villar

- S. [Nebulized colistin treatment of multi-resistant *Acinetobacter baumannii* pulmonary infection in critical ill patients]. *Med Intensiva* 2011; **35**: 226-231 [PMID: 21396739 DOI: 10.1016/j.medin.2011.01.013]
- 105 **Punpanich W**, Munsrichoom A, Srisarang S, Treeratweera-phong V. In vitro activities of colistin and ampicillin/sulbactam against *Acinetobacter baumannii*. *J Med Assoc Thai* 2011; **94** Suppl 3: S95-S100 [PMID: 22043760]
  - 106 **Betrosian AP**, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* 2008; **56**: 432-436 [PMID: 18501431 DOI: 10.1016/j.jinf.2008.04.002]
  - 107 **Tripodi MF**, Durante-Mangoni E, Fortunato R, Utili R, Zarrilli R. Comparative activities of colistin, rifampicin, imipenem and sulbactam/ampicillin alone or in combination against epidemic multidrug-resistant *Acinetobacter baumannii* isolates producing OXA-58 carbapenemases. *Int J Antimicrob Agents* 2007; **30**: 537-540 [PMID: 17851050 DOI: 10.1016/j.ijantimicag.2007.07.007]
  - 108 **Joshi SG**, Litake GM, Ghole VS, Niphadkar KB. Plasmid-borne extended-spectrum beta-lactamase in a clinical isolate of *Acinetobacter baumannii*. *J Med Microbiol* 2003; **52**: 1125-1127 [PMID: 14614072]
  - 109 **Hancock RE**. Resistance mechanisms in *Pseudomonas aeruginosa* and other nonfermentative gram-negative bacteria. *Clin Infect Dis* 1998; **27** Suppl 1: S93-S99 [PMID: 9710677 DOI: 10.1086/514909]
  - 110 **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/eid0808.020014]
  - 111 **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]
  - 112 **Bonomo RA**, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006; **43** Suppl 2: S49-S56 [PMID: 16894515 DOI: 10.1086/504477]
  - 113 **Jacoby GA**, Munoz-Price LS. The new beta-lactamases. *N Engl J Med* 2005; **352**: 380-391 [PMID: 15673804 DOI: 10.1056/NEJMra041359]
  - 114 **Litake GM**, Ghole VS, Niphadkar KB, Joshi SG. PER-1-type extended-spectrum beta-lactamase-producing *Acinetobacter baumannii* clinical isolates from India. *Int J Antimicrob Agents* 2009; **34**: 388-389 [PMID: 19589658 DOI: 10.1016/j.ijantimicag.2009.06.006]
  - 115 **Celenza G**, Pellegrini C, Caccamo M, Segatore B, Amicosante G, Perilli M. Spread of bla(CTX-M-type) and bla(PER-2) beta-lactamase genes in clinical isolates from Bolivian hospitals. *J Antimicrob Chemother* 2006; **57**: 975-978 [PMID: 16510850 DOI: 10.1093/jac/dkl055]
  - 116 **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]
  - 117 **Naas T**, Namdari F, Réglier-Poupert 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]
  - 118 **Naiemi NA**, Duim B, Savelkoul PH, Spanjaard L, de Jonge E, Bart A, Vandenbroucke-Grauls CM, de Jong MD. Widespread transfer of resistance genes between bacterial species in an intensive care unit: implications for hospital epidemiology. *J Clin Microbiol* 2005; **43**: 4862-4864 [PMID: 16145160 DOI: 10.1128/JCM.43.9.4862-4864.2005]
  - 119 **Livermore DM**, Woodford N. The beta-lactamase threat in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter*. *Trends Microbiol* 2006; **14**: 413-420 [PMID: 16876996 DOI: 10.1016/j.tim.2006.07.008]
  - 120 **Turner PJ**. Extended-spectrum beta-lactamases. *Clin Infect Dis* 2005; **41** Suppl 4: S273-S275 [PMID: 16032564 DOI: 10.1086/430789]
  - 121 **Vaze N**, Emery CL, Hamilton RJ, Brooks AD, Joshi SG. Patient demographics and characteristics of infection with carbapenem-resistant *Acinetobacter baumannii* in a teaching hospital from the United States. *Adv Infect Dis* 2013; **3**: 10-16 [DOI: 10.4236/aid.2013.31002]
  - 122 **Adams-Haduch JM**, Onuoha EO, Bogdanovich T, Tian GB, Marshall J, Urban CM, Spellberg BJ, Rhee D, Halstead DC, Pasculle AW, Doi Y. Molecular epidemiology of carbapenem-nonsusceptible *Acinetobacter baumannii* in the United States. *J Clin Microbiol* 2011; **49**: 3849-3854 [PMID: 21918019 DOI: 10.1128/JCM.00619-11]
  - 123 **Sen B**, Vaze N, Emery CL, Brooks AD, Joshi SG. Presence of blaOXA-51 like genes in carbapenem-resistant *Acinetobacter baumannii* in hospitalized patients in Philadelphia, PA. 2012 International Symposium on Molecular Medicine and Infectious Diseases, 2012 Jun 19-21; Drexel University, College of Medicine, Philadelphia
  - 124 **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]
  - 125 **Rolain JM**, Diene SM, Kempf M, Gimenez G, Robert C, Raoult D. Real-time sequencing to decipher the molecular mechanism of resistance of a clinical pan-drug-resistant *Acinetobacter baumannii* isolate from Marseille, France. *Antimicrob Agents Chemother* 2013; **57**: 592-596 [PMID: 23070160 DOI: 10.1128/AAC.01314-12]
  - 126 **Huang H**, Yang ZL, Wu XM, Wang Y, Liu YJ, Luo H, Lv X, Gan YR, Song SD, Gao F. Complete genome sequence of *Acinetobacter baumannii* MDR-TJ and insights into its mechanism of antibiotic resistance. *J Antimicrob Chemother* 2012; **67**: 2825-2832 [PMID: 22952140 DOI: 10.1093/jac/dks327]
  - 127 **Szabó D**, Szentandrassy J, Juhász Z, Katona K, Nagy K, Rókusz L. Imported PER-1 producing *Pseudomonas aeruginosa*, PER-1 producing *Acinetobacter baumannii* and VIM-2-producing *Pseudomonas aeruginosa* strains in Hungary. *Ann Clin Microbiol Antimicrob* 2008; **7**: 12 [PMID: 18513394 DOI: 10.1186/1476-0711-7-12]
  - 128 **Vahaboglu H**, Oztürk R, Aygün G, Coşkuncan F, Yaman A, Kaygusuz A, Leblebicioğlu H, Balık I, Aydın 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]
  - 129 **Yong D**, Shin JH, Kim S, Lim Y, Yum JH, Lee K, Chong Y, Bauernfeind A. High prevalence of PER-1 extended-spectrum beta-lactamase-producing *Acinetobacter* spp. in Korea. *Antimicrob Agents Chemother* 2003; **47**: 1749-1751 [PMID: 12709353 DOI: 10.1128/AAC.47.5.1749-1751.2003]
  - 130 **Poirel L**, Karim A, Mercat A, Le Thomas I, Vahaboglu H, Richard C, Nordmann P. Extended-spectrum beta-lactamase-producing strain of *Acinetobacter baumannii* isolated from a patient in France. *J Antimicrob Chemother* 1999; **43**: 157-158 [PMID: 10381117]



- 131 **Naas T**, Bogaerts P, Bauraing C, Degheltre Y, Glupczynski Y, Nordmann P. Emergence of PER and VEB extended-spectrum beta-lactamases in *Acinetobacter baumannii* in Belgium. *J Antimicrob Chemother* 2006; **58**: 178-182 [PMID: 16670107 DOI: 10.1093/jac/dkl178]
- 132 **Naas T**, Nordmann P, Heidt A. Inter-country transfer of PER-1 extended-spectrum beta-lactamase-producing *Acinetobacter baumannii* from Romania. *Int J Antimicrob Agents* 2007; **29**: 226-228 [PMID: 17137755 DOI: 10.1016/j.ijantimicag.2006.08.032]
- 133 **Carbonne A**, Naas T, Blanckaert K, Couzigou C, Cattoen C, Chagnon JL, Nordmann P, Astagneau P. Investigation of a nosocomial outbreak of extended-spectrum beta-lactamase VEB-1-producing isolates of *Acinetobacter baumannii* in a hospital setting. *J Hosp Infect* 2005; **60**: 14-18 [PMID: 15823651 DOI: 10.1016/j.jhin.2004.07.027]
- 134 **Robledo IE**, Aquino EE, Vázquez GJ. Detection of the KPC gene in *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* during a PCR-based nosocomial surveillance study in Puerto Rico. *Antimicrob Agents Chemother* 2011; **55**: 2968-2970 [PMID: 21444702 DOI: 10.1128/AAC.01633-10]
- 135 **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]
- 136 **Higgins PG**, Lehmann M, Seifert H. Inclusion of OXA-143 primers in a multiplex polymerase chain reaction (PCR) for genes encoding prevalent OXA carbapenemases in *Acinetobacter* spp. *Int J Antimicrob Agents* 2010; **35**: 305 [PMID: 20022220 DOI: 10.1016/j.ijantimicag.2009.10.014]
- 137 **Landman D**, Babu E, Shah N, Kelly P, Olawole O, Bäcker M, Bratu S, Quale J. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. *J Antimicrob Chemother* 2012; **67**: 1427-1431 [PMID: 22378678 DOI: 10.1093/jac/dks063]
- 138 **Hamouda A**, Evans BA, Towner KJ, Amyes SG. Characterization of epidemiologically unrelated *Acinetobacter baumannii* isolates from four continents by use of multilocus sequence typing, pulsed-field gel electrophoresis, and sequence-based typing of bla(OXA-51-like) genes. *J Clin Microbiol* 2010; **48**: 2476-2483 [PMID: 20421437 DOI: 10.1128/JCM.02431-09]
- 139 **Figueiredo S**, Bonnin RA, Poirel L, Duranteau J, Nordmann P. Identification of the naturally occurring genes encoding carbapenem-hydrolysing oxacillinases from *Acinetobacter haemolyticus*, *Acinetobacter johnsonii*, and *Acinetobacter calcoaceticus*. *Clin Microbiol Infect* 2012; **18**: 907-913 [PMID: 22128805 DOI: 10.1111/j.1469-0691.2011.03708.x]
- 140 **Kusradze Ia**, Diene SM, Goderdzishvili M, Rolain JM. Molecular detection of OXA carbapenemase genes in multidrug-resistant *Acinetobacter baumannii* isolates from Iraq and Georgia. *Int J Antimicrob Agents* 2011; **38**: 164-168 [PMID: 21616644 DOI: 10.1016/j.ijantimicag.2011.03.021]
- 141 **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]
- 142 **He C**, Xie Y, Zhang L, Kang M, Tao C, Chen Z, Lu X, Guo L, Xiao Y, Duo L, Fan H. Increasing imipenem resistance and dissemination of the ISAba1-associated blaOXA-23 gene among *Acinetobacter baumannii* isolates in an intensive care unit. *J Med Microbiol* 2011; **60**: 337-341 [PMID: 21127157 DOI: 10.1099/jmm.0.022681-0]
- 143 **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 DOI: 10.1111/j.1469-0691.2007.01825.x]
- 144 **Di Popolo A**, Giannouli M, Triassi M, Brisse S, Zarrilli R. Molecular epidemiological investigation of multidrug-resistant *Acinetobacter baumannii* strains in four Mediterranean countries with a multilocus sequence typing scheme. *Clin Microbiol Infect* 2011; **17**: 197-201 [PMID: 20456455 DOI: 10.1111/j.1469-0691.2010.03254.x]
- 145 **Sevillano E**, Fernández E, Bustamante Z, Zabalaga S, Rosales I, Umaman A, Gallego L. Emergence and clonal dissemination of carbapenem-hydrolysing OXA-58-producing *Acinetobacter baumannii* isolates in Bolivia. *J Med Microbiol* 2012; **61**: 80-84 [PMID: 21873380 DOI: 10.1099/jmm.0.032722-0]
- 146 **Sung JY**, Kwon KC, Park JW, Kim YS, Kim JM, Shin KS, Kim JW, Ko CS, Shin SY, Song JH, Koo SH. [Dissemination of IMP-1 and OXA type beta-lactamase in carbapenem-resistant *Acinetobacter baumannii*]. *Korean J Lab Med* 2008; **28**: 16-23 [PMID: 18309251 DOI: 10.3343/kjlm.2008.28.1.16]
- 147 **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]
- 148 **Pfeifer Y**, Witte W, Holfelder M, Busch J, Nordmann P, Poirel L. NDM-1-producing *Escherichia coli* in Germany. *Antimicrob Agents Chemother* 2011; **55**: 1318-1319 [PMID: 21189341 DOI: 10.1128/AAC.01585-10]
- 149 **Fiett J**, Baraniak A, Mrówka A, Fleischer M, Drulis-Kawa Z, Naumiuk L, Samet A, Hryniewicz W, Gniadkowski M. Molecular epidemiology of acquired-metallo-beta-lactamase-producing bacteria in Poland. *Antimicrob Agents Chemother* 2006; **50**: 880-886 [PMID: 16495246 DOI: 10.1128/AAC.50.3.880-886.2006]
- 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 **Tognim MC**, Gales AC, Pentead 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 DOI: 10.1086/504356]
- 152 **Zhou Z**, Du X, Wang L, Yang Q, Fu Y, Yu Y. Clinical carbapenem-resistant *Acinetobacter baylyi* strain coharboring blaSIM-1 and blaOXA-23 from China. *Antimicrob Agents Chemother* 2011; **55**: 5347-5349 [PMID: 21876057 DOI: 10.1128/AAC.00425-11]

**P- Reviewers** Abraham WR, Borgmann S, Ergin MA  
**S- Editor** Wen LL **L- Editor** A **E- Editor** Lu YJ





Published by **Baishideng Publishing Group Co., Limited**  
Flat C, 23/F., Lucky Plaza,  
315-321 Lockhart Road, Wan Chai, Hong Kong, China  
Telephone: +852-6555-7188  
Fax: +852-3177-9906  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
<http://www.wjgnet.com>

