Review Article

Carbapenem resistance in *Acinetobacter baumannii*: the molecular epidemic features of an emerging problem in health care facilities

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Abstract

Acinetobacter baumannii is an opportunistic gram-negative pathogen with increasing relevance in a variety of nosocomial infections especially among intensive-care-unit (ICU) patients. Carbapenems have been widely used to treat serious multidrug-resistant *A. baumannii* infections; however, incidences of carbapenem-resistant *A. baumannii* are rising in several parts of the world and large and sustained outbreaks caused by such bacteria have been described. Carbapenem-resistant *A. baumannii* epidemics are sustained by clusters of highly similar strains that successfully spread among different cities and countries; their resistance phenotype is mainly due to the acquisition of carbapenem-hydrolyzing class D β-lactamase (CHDL) genes flanked by insertion sequence (IS) elements. Multi-facility outbreaks can be also sustained by inter-hospital transfer of colonized patients. Here, we review the global epidemiology of carbapenem-resistant *A. baumannii*, with the emphasis on the molecular epidemiology and genetic characterization of carbapenem resistance in epidemic strains.

Key words: *Acinetobacter baumannii*, nosocomial outbreaks, genotyping, carbapenemases

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Introduction

Acinetobacter spp. are glucose-non fermentative gram-negative coccobacilli that have emerged in recent years as a cause of healthcare-associated infections [1,2]. Considered to be commensals of low-grade pathogenicity, i.e. opportunistic microorganisms, *Acinetobacter* were frequently ignored in the 1970s whenever isolated from clinical specimens [1]. The genus *Acinetobacter* currently contains up to 32 described named and unnamed (genomic) species [1]. *Acinetobacter baumannii*, genomic species 3 and 13TU, three of the most clinically relevant species, are genetically and phenotypically very similar to an environmental species, *A. calcoaceticus*, and are therefore grouped together into the so-called *A. calcoaceticus-A. baumannii* (Acb) complex [1]. Because phenotypic identification of *Acinetobacter* isolates to the species level has proven to be insufficient, several genotypic methods have been developed for genomic species identification, that include amplified 16S rRNA gene restriction analysis (ARDRA), high-resolution fingerprint analysis by amplified fragment length polymorphism (AFLP), or sequence analysis of the 16S-23S rRNA gene spacer region [1,3,4]. However, genotypic methods for species identification are often unavailable in developing countries, where *Acinetobacter* are frequently isolated but identified only at genus level. The species that is most commonly involved in hospital infections is *A. baumannii*, which causes a variety of health-care associated infections, comprising bacteremia, urinary tract infection, surgical-site infection, and nosocomial and ventilator-associated pneumonia, especially in intensive-care-unit (ICU) patients [1,2,5-7]. The rates of recovery of *A. baumannii* from natural environments and its incidence in the community are low, while its rate of carriage by hospitalized patients is high and its occurrence in the hospital setting is frequent [1]. *A. baumannii* has simple growth requirements and can survive in dry conditions. This might contribute to the fitness of *A. baumannii* in the hospital environment, which represents the main reservoir of the bacterium [1].

Carbapenem resistance mechanisms in *A. baumannii*

Resistance to antimicrobial agents may be the main advantage of *A. baumannii* in the nosocomial environment. Multidrug-resistant isolates of *A. baumannii* have been reported increasingly during the last decade, probably as a consequence of extensive use of antimicrobial agents in western countries [2,8]. Also, as recently demonstrated by a retrospective, matched cohort study, patients with infection by multidrug-resistant *Acinetobacter* show higher mortality rate and length of hospitalization than patients with infection by susceptible *Acinetobacter* [5].

Mounting evidence indicates that *A. baumannii* possesses a broad range of mechanisms of resistance to all existing antibiotic classes as well as a prodigious capacity to acquire new determinants of resistance [1,2] Genome sequence analysis of six *A. baumannii* clinical strains has shown the presence of a resistance island with a variable composition of resistance genes interspersed with transposons, integrons, and other mobile genetic elements in three of them [9-11]. Also, plasmids carrying resistance genes and/or resistance determinants involved in horizontal gene transfer have been described in several *A. baumannii* strains [12-19].

The broad-spectrum β-lactam antibiotics, carbapenems, were introduced by 1985 and have been for years the most important agents for the treatment of infections caused by multidrug-resistant *A. baumannii*. Carbapenem resistance in *Acinetobacter* is now observed increasingly worldwide, and constitutes a sentinel event for emerging antimicrobial resistance [2,12]. Carbapenem-resistant isolates of *A. baumannii* are usually resistant to all classes of antimicrobials, and show intermediate resistance to rifampin, while usually retaining susceptibility to tigecycline and colistin [2,12,20]. Resistance against carbapenems is, in itself, considered sufficient to define an isolate of *A. baumannii* as highly resistant [12]. The resistance of *A. baumannii* to carbapenems can be mediated by one of the resistance mechanisms that are known to occur in bacteria, including enzymatic inactivation, active efflux of drugs, and modification of target sites (Table 1). The production of carbapenem-hydrolizing beta-lactamases is the most common mechanism responsible for carbapenem resistance in *A. baumannii*. Several carbapenem-hydrolyzing β-lactamases have been identified so far in *A. baumannii*. These include metallo-β-lactamases (VIM-, IMP- and SIM-types), which have been sporadically reported in some parts of the world and have been associated with class 1 integrons [2,7,12]. Nevertheless, the most widespread carbapenemases in *A. baumannii* are class D β-lactamases. Three main acquired carbapenem-hydrolysing class D oxacillinase (CHDL) gene clusters have been identified either in the chromosome or in plasmids of *A. baumannii* strains, represented by the $bla_{\text{OXA-23}}$-, $bla_{\text{OXA-24/40}}$-, and $bla_{\text{OXA-58}}$-like genes [12]. Different insertion sequence (IS) elements at the 5' and/or the 3' end of $bla_{\text{OXA-23}}$-, and $bla_{\text{OXA-58}}$-like genes, such as IS*Aba1*, IS*Aba2*, IS*Aba3*, or IS*18*, have been demonstrated to regulate their expression [12,13,15-17]. Also, it has been recently demonstrated that the IS*Aba1* element is capable of transposition in *E. coli* and of mobilizing an antibiotic resistance gene [18]. In addition to these CHDL genes, the chromosomal $bla_{\text{OXA-51-like}}$ gene, intrinsic to *A. baumannii* species, has been demonstrated to confer carbapenem resistance when an IS*Aba1* element is inserted upstream of the gene [19]. Reduced susceptibility to carbapenems has also been associated with the modification of penicillin-binding proteins and porins or with upregulation of the AdeABC efflux system, and it has been suggested that the interplay of different mechanisms might result in high-level carbapenem resistance in *A. baumannii* (Table 1) [21-23].

Global epidemiology of carbapenem-resistant *Acinetobacter baumannii*

Carbapenem resistance in *A. baumannii* is now an emerging issue worldwide [2]. Surveillance studies indicate that the percentage of carbapenem-resistant isolates gradually increased over the last ten years in Europe, North America, and Latin America [2]. Numerous outbreaks of carbapenem-resistant *A. baumannii* were reported from hospitals in Northern Europe (Spain, Portugal, France, the United Kingdom (UK), the Netherlands, Czech Republic, Poland) [1,2, 24-29], Southern Europe and the Middle East (Bulgaria, Greece, Italy, Turkey, Lebanon, Israel, Iran, Iraq and United Arab Emirates) [2,6-8,10,12,14,16,17,30-35], North America and Latin America (Argentina, Brazil, Chile and Colombia) [2,36,37], Tunisia and South Africa [38,39], China, Taiwan, Singapore, Hong Kong, Japan, South Korea [2,40,41], and Australia [42] and from areas as remote as French Polynesia [43]. In the majority of cases, one or two epidemic strains were detected in a given hospital. Transmission of such strains was

Table 1. Carbapenem resistance mechanisms in *A. baumannii*.

Mechanism or responsible structure	Note	References
β-lactam hydrolysis		
IMP-1, -2, -4, -5, -6, -11 VIM-2, SIM-1	Class B metallo beta-lactamases. Class 1 integron-associated genes.	2,12
OXA-23 cluster	Class D beta-lactamases. Chromosomal or plasmid genes flanked by IS elements.	2,12,13,17
OXA-24/40 cluster	Class D beta-lactamases. Chromosomal or plasmid genes.	2,12
OXA-58 cluster	Class D beta-lactamases. Plasmid or chromosomal genes flanked by IS elements.	12-16
OXA-51cluster	Chromosomal class D beta-lactamase intrinsic to *A. baumannii*. Confers carbapenem resistances if IS elements are inserted upstream of the gene	2,19
Changes in outer-membrane proteins (OMPs)		
CarO	26 kDa OMP implicated in drug influx	21
33 to 36-kDa OMP OprD-like OMP	Other OMPs associated with carbapenem resistance	2,12
Target alteration		
Altered penicillin-binding proteins	Reduced PBP-2 expression	22

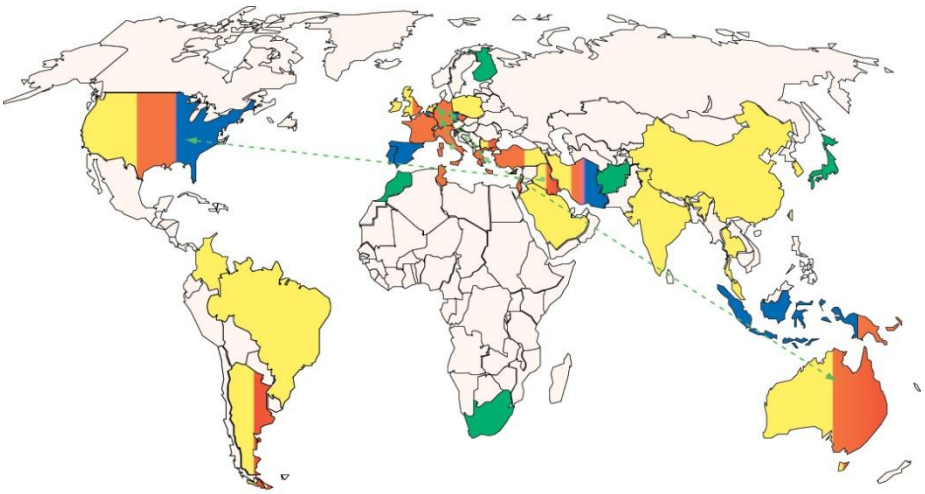
observed between hospitals in the same city and also on a national scale [1,2,6,12,24-27,29,30,3,38,42,44-46] and a direct epidemiological link was established in several cases [6,25,28,29,38,42,44-46]. The inter-hospital transfer of colonised patients was demonstrated during multi-facility outbreaks that occurred in the Netherlands [25], Italy [6], South Africa [38], and Tunisia [39]. The international transfer of patients colonised by carbapenem-resistant *A. baumannii* was also reported [28, 29, 42]. More recently, several cases of United Kingdom and US military and nonmilitary personnel returning from operations in Iraq and Afghanistan and harbouring infections caused by carbapenem-resistant *A. baumannii* were reported [44-46] (Figure 1).

Outbreaks caused by carbapenem-resistant *A. baumannii* have also been observed in developing countries such as Morocco, Thailand, India, and Indonesia [47,41]. Furthermore, infections caused by *Acinetobacter* spp. without specifying whether they are caused by carbapenem-resistant strains have been reported in Africa (Lagos, Nigeria) and several Asian countries including Nepal [48-50].

Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii*

Genotypic characterization of carbapenem-resistant *A. baumannii* strains showed the occurrence of $bla_{\text{OXA-23}}$-, $bla_{\text{OXA-24/40}}$-, or $bla_{\text{OXA-58}}$-like genes in multiple isolates from the same hospital or among different hospitals worldwide [2,12,13,33,34,43,52]. $bla_{\text{OXA-23}}$ was mostly detected in isolates from Asian countries [41], but was also reported in South America [36,37] and Europe [12,17,31,51]; $bla_{\text{OXA-58}}$ was frequently found in Europe [6,7,10,14,30,33,16,30-35,51]. $bla_{\text{OXA-24/40}}$ was mostly found in the Iberian peninsula and Asia, but also detected in Iran, Belgium, Czech Republic and the United States of America (USA) [2,26,27,41,44,51,52] (Figure 1). Molecular epidemiology of *A. baumannii* strains responsible for outbreaks that occurred in several European hospitals revealed clusters of highly similar strains, which were defined as European clones I and II [1,2] and corresponded to sequence type (ST) groups 2 and 1, respectively, identified by sequence-based typing [53]. A recent study on a collection of 96 carbapenem-resistant *A. baumannii* strains collected in 17 European countries assigned 85% of them to sequence type (ST) groups 1 and 2 by multiple PCRs [51]. The prevalence of carbapenem-resistant epidemic *A. baumannii* strains belonging to ST group 1 was also demonstrated in Italy and Greece [30,33] along with the spread of a prevalent clone isolated with identical pulsed field gel electrophoresis (PFGE) profiles in two hospitals in Naples, Italy, and in three hospitals in three distinct Greek cities [33]. The circulation of distinct carbapenem-resistant *A.*

Figure 1



Geographic distribution and genetic characterization of carbapenem-resistant *A. baumannii*. Countries reporting carbapenem-resistant *A. baumannii* outbreaks producing OXA-23-, OXA-24/40-, and/or OXA-58-type enzymes are indicated by yellow, blue, and red colours, respectively. Countries reporting carbapenem-resistant *A. baumannii* outbreaks in which the OXA-type enzyme has not been identified are indicated by green colour. Green arrows indicate hospital transfer of colonized/infected patients by carbapenem-resistant *A. baumannii* between different countries.

baumannii genotypes belonging to ST group 2 in Greece and in Lebanon, and to two novel ST groups 4 and 5 in different Greek and Turkish cities, was also shown in the same study [33]. The $bla_{\text{OXA-58}}$ gene flanked by IS elements was present in all carbapenem-resistant genotypes analyzed from hospitals in Greece, Italy, Lebanon, and Turkey [7,16,33] (Figure 1). Of note, each of the IS elements flanking the 5' end of $bla_{\text{OXA-58}}$ occurred in strains of distinct ST groups and PFGE profiles isolated in the same geographic region. Thus, IS*Aba2* element was detected in Greece and Italy, IS*18* in Lebanon and Turkey, and IS*Aba1* in Turkey and Italy, suggesting that they might have been acquired through horizontal gene transfer [33]. In further support of this hypothesis, plasmid-borne $bla_{\text{OXA-58}}$ has been found in the majority of carbapenem-resistant *A. baumannii* strains isolated in Europe [6,7,10,13,14,16,33]. The spread of carbapenem-resistant *A. baumannii* carrying the $bla_{\text{OXA-58}}$ gene might had also been contributed by international transfer of colonised patients, as recently demonstrated from Greece to Belgium [28], Greece to Australia [42], and Iraq to USA military services [44] (Figure 1).

Conclusions

Outbreaks of carbapenem-resistant *A. baumannii* are increasingly reported in several parts of the world that also include developing countries. They are sustained by clusters of highly similar strains that successfully spread among different cities and countries and are selected because of the acquisition of CHDLs genes flanked by IS elements. Multi-facility *A. baumannii* outbreaks can be also sustained by inter-hospital transfer of colonized patients. This emphasizes the need to adopt surveillance and infection control programmes to prevent colonisation and infection by multidrug-resistant *A. baumannii* in the hospital setting. These programmes would include the study of global epidemiology of multidrug-resistant *A. baumannii* using molecular typing of bacterial isolates and characterization of antibiotic resistance in order to control the spread of *A. baumannii* infections over a wide geographic region.

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