Mini Review

# Carbapenem-resistant *Acinetobacter baumannii* in Taiwan

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***Acinetobacter baumannii*** **has emerged recently as a major cause of health care-associated infections due to the extent of its antimicrobial resistance and its propensity to cause nosocomial infectious outbreaks. Carbapenems have been used to treat multidrug-resistant *A. baumannii* infections. However, the incidences of carbapenem-resistant *A. baumannii* are rising in Taiwan and many other countries. Clonal spread of cabapenem-resistant *A. baumannii* via intra-hospitals or inter-hospitals has been reported; their resistance phenotype is mainly due to the acquisition of oxacillin-hydrolyzing-β-lactamase (OXA) genes. The rapid emergence and increase of imipenem resistance in *A. baumannii* in different areas of Taiwan is contributed to by a variety of mechanisms. The finding of different resistant gene determinants could not explain the phenotypic variation in drug susceptibility. More researches would be required to solve the gaps from resistant genes to phenotypic dynamics by functional genomic studies via the products of genome using high throughput analytic technologies.**

***Key words*****: carbapenem, *Acinetobacter baumannii*, *bla*$_{OXA}$ genes**

## Introduction

*Acinetobacter* spp. is a group of nonfermentative, Gram negative, non-motile, oxidase-negative bacilli. In the past, these microorganisms were considered to be opportunistic pathogens with low grade pathogenicity whenever isolated from clinical specimens [1]. Recently, the combination of its environmental resilience and its wide range of resistant determinants renders it as an important cause of healthcare-associated infections [2]. The genus currently contains up to 32 species; 17 named species have been recognized and 15 genomic species (gen. sp.) have been delineated by DNA-DNA hybridization [3]. Most of *Acinetobacter* species have used to be identified by the phenotypic system [4,5]. However, four *Acinetobacter* species, including *Acinetobacter baumannii,* genomic species 3, 13 TU, three of the clinical relevant species, and *Acinetobacter calcoaceticus*, could not be differentiated well by this system, and are therefore grouped into so-called *A. calcoaceticus-A. baumannii* (Acb) complex [1]. Because the performance of commercial systems for species identification of *Acinetobacter* in clinical microbiological laboratory is unsatisfactory, several genotypic fingerprinting methods for genomic species identification, including ribotyping, amplified fragment length polymorphism, amplified 16S ribosomal DNA (rDNA) restriction analysis (ARDRA), or 16S-23S rRNA gene spacer determination have been developed [2,3,6]. Of all the *Acinetobacter* spp., *Acinetobacter baumannii* is the most common one involved in hospital infections, comprising ventilator-associated pneumonia, urinary tract infections and bacteremia. Despite carbapenems, mainly imipenem and meropenem, was effective for the treatment of *A. baumannii* infections previously [3,7], the increasing find of carbapenem-resistant *A. baumannii* (CRAB) in Taiwan has

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become a frightening reality nowadays[8]. This review summarizes the present status of CRAB in Taiwan, with the emphasis on molecular epidemiology and genetic characterization of carbapenem resistance in clinical strains in Taiwan.

## Surveillance study of antimicrobial susceptibility in *A. baumannii*

Resistance to antimicrobial agents may be the main advantage of *A. baumannii* in causing large-scale nosocomial infectious outbreaks [1]. Multidrug resistance of *A. baumannii* to many commonly used antibiotics has been increasingly reported worldwide as shown in Table 1 [2] . Two nationwide surveillance programs, the Taiwan Surveillance of Antimicrobial Resistance (TSAR) and the surveillance for Multicenter Antimicrobial Resistance in Taiwan (SMART) program, were initiated in order to monitor the antimicrobial resistance status in Taiwan [9-11]. Besides, a long-term surveillance program within a medical center [12] or among several hospitals [13] were also performed in recent years. Those studies showed that the high resistant rates of most antibiotics to *A. baumannii* have been found throughout the island [8]. In 1988, imipenem was first introduced into Taiwan and has been used widely in the treatment of bacterial infections in teaching hospitals since then [12]. The prevalence of carbapenem resistance in *A. baumannii* was low before 2000. However, up to 25-35% of imipenem resistance to *A. baumannii* was demonstrated in 2005 [11]. One of our studies in 2007 showed that 60% of imipenem non-susceptibility was found in three regional hospitals in northern Taiwan [14]. This result and the global surveillance data of SENTRY Antimicrobial Surveillance program in 2004 [15] implicated that the high prevalence of imipenem resistance in *A. baumannii* is now a global problem.

## Carbapenem resistance mechanisms in *A. baumannii*

The mechanisms underlying carbapenem resistance in *A. baumannii* are (i) carbapenem hydrolysis by carbapenemases [16], and (ii) changes in outer membrane proteins (OMP) and penicillin-binding proteins (PBP) [17-21] as shown in Table 2.

## Carbapenemases

Beta-lactamase-hydrolyzing enzymes belong to two major molecular families, distinguished by the hydrolytic mechanism at the active site [16]. One group of beta-lactamases, including molecular classes A, C, and D, contains the beta-lactamase with serine at their active site, whereas another group of beta-lactamases, molecular class B beta-lactamases, are all metalloenzymes with an active site zinc [22]. Carbapenemases represent the most versatile family of beta-lactamases, with a broad spectrum unrivalled by other beta-lactamase-hydrolyzing enzymes. At present, two classes of beta-lactamases, class B (metallo-β-lactamases) and cass D (oxacillin-hydrolyzing β-lactamases) have been involved in carbapenem resistance of *A. baumannii* [23].

**Table 1.** Survey of global susceptibility of *A. baumannii* to imipenem

| Geographic area | Location/study[a] | Year | No. of hospitals | IMP non-susceptible(%)[b] | Reference |
|---|---|---|---|---|---|
| Taiwan | Hospital isolates | 1993-2000 | 1 | 6—22 | [12] |
| | Hospital isolates/TSAR | 2000 | 21 | 2 | [9] |
| | Hospital isolates/SMART | 2000 | 12 | 0-19 | [49] |
| | RCWs | 2005 | 17 | 34 | [13] |
| | ICUs/SMART | 2005 | 10 | 25 | [11] |
| | hospital isolates | 2006-2008 | 3 | 19-61 | [14] |
| North America | Hospital isolates/SENTRY | 2001-2004 | 42 | 11 | [15] |
| Latin America | Hospital isolates/SENTRY | 2001-2004 | 12 | 16 | [15] |
| Europe | Hospital isolates/SENTRY | 2001-2004 | 30 | 27 | [15] |
| Asia-Pacific region | Hospital isolates/SENTRY | 2001-2004 | 17 | 26 | [15] |

[a] ICU, Intensive Care Unit; TSAR, Taiwan Surveilance of Antimicrobial Resistance; SMART, Surveillance for Multicenter Antimicrobial Resistance in Taiwan; RCWs, Respiratory care wards; SENTRY, SENTRY Antimicrobial Surveillance Program.

[b] IMP, imipenem

**Table 2.** Carbapenem resistance mechanisms in *A. baumannii*

| Mechanism | Gene structure or function | Reference |
|---|---|---|
| **β-lactam hydrolysis** | | |
| Class B metallo beta-lactamases | | |
| IMP-1, -2, -4, -5, -6, -11 | Class1 integron-associated genes. | [1,7] |
| VIM-2 | Class1 integron-associated genes. | [1,7] |
| SIM-1 | Class1 integron-associated genes. | [1,7] |
| Class D beta-lactamases | | |
| OXA-23 cluster | Chromosomal or plasmid genes flanked by IS elements. | [28] |
| OXA-24/40 cluster | Chromosomal or plasmid genes. | [28] |
| OXA-58 cluster | Plasmid or chromosomal genes flanked by IS elements. | [28] |
| OXA-51 cluster | Chromosomal enzyme intrinsic to *A. baumannii*. | [30] |
| **Changes in ourter-membrane proteins (OMPs)** | | |
| CarO | 26 kDa OMP implicated in drug influx | [17] |
| 22 to 36 KDa OMP | Other OMPs associated with carbapenem resistance | [20] |
| 37-, 44-, and 47 KDa OMP | | [21] |
| OprD-like OMP | | [19] |
| **Target alteration** | | |
| Altered penicillin-binding proteins | Reduced PBP-2 expression | [18] |

The metallo-β-lactamases (MBL), which were located in chromosome or transferable plasmids, were widely distributed in Gram negative bacteria such as *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [16]. The chromosomal enzymes were found in several opportunistic pathogens and were not frequently associated with serious nosocomial infections [24-25]. Nevertheless, the transferable families of metalloenzymes are directly associated with the global prevalence of the producing species resistance to carbapenem [16]. The most common found transferable MBL families include VIM, IMP, GIM and SIM enzymes, which are located within a variety of integron structures, which they have been incorporated as gene cassettes [1,7]. When these integrons become associated with plasmids or transposons, the horizontal transfer of those MBL genes is facilitated between bacteria. Another MBL family consist of SPM enzymes that are not a part of an integron but instead is associated with common regions that contain a new type of transferable structure [26]. Compared to SPM, GIM and SIM MBLs that have not been spread beyond the countries of origins, IMP and VIM are highly prevalent worldwide [16].

Oxacillin-hydrolyzing (OXA) β-lactamases is one of the most prevalent plasmid-encoding carbapenemases, mainly found in the *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* [27]. Currently, nine major subgroups of OXA carbapenemases, based on amino acid homologies, are identified [28]. Four subgroups of OXA, including OXA-23-like, OXA-24-like, OXA-51-like and OXA-58-like, are prevalent in *A. baumannii* and have been reported in outbreaks of several countries [29]. Besides, OXA-51-like enzymes have been found to be intrinsic resistant determinants in *A. baumannii* strains [30].

## Changes in OMP and PBP

Reduced susceptibility to carbapenems has been demonstrated with the modification of PBPs and OMPs in *A. baumannii* [17,18,19]. Three kinds of OMPs, including CarO [17], 22 to 36 KDa OMP [20]; 37-, 44-, and 47 KDa OMP [21] and oprD-like OMP [19], have participated in the resistance to carbapenems. The reduced expression of PBP-2 lead to carbapenem resistance has also been reported [18].

## Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii*

The spread of imipenem-resistant *A. baumannii* carrying $bla_{OXA}$ genes from the same hospitals or among different hospitals worldwide has been recently documented [1,7]. Outbreaks due to *Acinetobacter* spp. clones producing OXA-23 carbapenemase have been reported in Asian countries [31], South America [32] and Europe [7]; $bla_{OXA\text{-}24\text{-}like}$was mostly found in Asia, Iran, Belgium, Czech Republic and the United State of America

(USA)[1]; $bla_{OXA-58}$ was mostly detected in Europe [1]. Two clones, European clone I and II, were predominant in the outbreaks that occurred in several European hospitals [1,3]. In Taiwan, the SMART program during 2005 demonstrated inter-hospital dissemination of some extensively drug-resistant (XDR) *A. baumannii* clones [11]. The clonal spread of XDR *A. baumannii* was restricted to hospitals located in northern, central and southern Taiwan. One of our previous studies also revealed that there was no evidence of inter-hospital transmission of *A. baumannii* between the three hospitals located in these three Taiwanese regions [33]. However, in another study conducted in three Taiwan medical centers, the predominant clone in the three regions belonged to one island-wide epidemic clone [34]. Besides, we also found that local spread of MDR A. *baumannii* among nearby hospitals is present and may contribute to the dissemination of MDR *A. baumannii* in Taiwan [35].

The local dissemination of MDR *A. baumannii* was also supported by several studies in Taiwan. Clonal spread of $bla_{OXA-72}$ genes in *A. baumannii* has been observed in a hospital in southern Taiwan [36], whereas the prevalence of clonal-related $bla_{OXA-23}$-carrying MDR *A. baumannii* was found in central and northern Taiwan [37,38]. In another study of a university hospital about imipenem-resistant *A. baumannii* in southern Taiwan, 43% of the isolates possessed MBL genes [39]. However, none of MBL genes could be detected in our study [33]. All of the above study results implied that the rapid emergence and increase of imipenem resistance in *A. baumannii* in different areas of Taiwan is contributed to by a variety of mechanisms.

## The gap from antimicrobial resistant determinants to phenotypic characterization: a hint from the study of integron

Dissemination and characterization of integrons among *A. baumannii* have been described in previous studies [34]. Integrons are genetic assembly platforms - DNA elements that acquire open reading frames embedded in exogenous gene cassettes that are converted to functional genes upon correct expression [40]. These DNA elements have been frequently identified in multidrug resistant strains and are located on the chromosome, in plasmids or in transposons [41]. Resistance to carbapenem by carbapenem-hydrolyzing oxacillinase, metallo-β-lactamases and extended-spectrum β-lactamase has been reported to be conferred to *A. baumannii* strains via integrons [40]. In one of our studies, we investigated the relationship between the presence and types of integrons and antimicrobial susceptibility patterns in 134 non-duplicated *A. baumannii* isolates [42]. Of these *A. baumannii* isolates, 54.5% (73/134) carried class 1 integrons. Only two types of gene cassette arrays, *aacA4-catB8-aadA1* and *aacC1-orfP-orf-P-orfQ-aadA1,* were identified. Susceptibility data showed that the strains carrying integrons were significantly more resistant to all tested antibiotics except ampicillin/sulbactam and imipenem. These findings implicated that the presence of integrons in *A. baumannii* is a marker of multidrug resistance. But the study of integron gene cassettes in *A. baumannii* has not explained well the phenotypic expression in antimicrobial resistance.

The gaps from resistant gene determinants to phenotypic characterization remain unsolved. Bratu et al. [43] demonstrated that multiple factors have contributed to antimicrobial resistance in clinical isolates of *A. baumannii*. Data from Yan et al. [44] show a high distribution of integrons, transposons, resistant gene determinants and efflux pumps in genotypically related and unrelated MDRAB strains, emphasizing the multitude of resistance genes that *A. baumannii* is capable of possessing and the potential horizontal gene transfer between polyclonal MDRAB strains. However, the location of these genes in the chromosome and the way their transmission across those bacteria leading to multidrug resistance has remained to be solved. A recent study describing the genome sequence of both susceptible (SDF) and resistant (AYE) isolates of *A. baumannii* has shed light on the abundance of resistant genes in this organisms [45]. Fournier et al. [45] identified an 86-kb AbaR1 resistant island in AYE that contained a cluster of 45 resistance genes in the MDR isolates. Besides the resistant genes, mobile genetic elements (transposon) and integrons were also found in this island region. A contemporary study in the genome of *A. baumannii* ATCC 19606 [46] showed that a significant fraction (17%) of the open reading frames were located in 28 putative alien islands, indicating that the genome acquired a large number of foreign DNA. Another study about the resistant island sequence of ACICU isolates of *A. baumannii* showed that part of the carbapenem-resistant genes were from AbaR1 region [47]. A more detail examination of resistant island determinants in close-related strains concluded that highly dynamic resistant gene repertoires suggest rapid evolution of drug resistance in *A. baumannii* [48]. All these studies imply that a phenotypic resistance would be contributed by multiple resistant factors in *A. baumannii*.

## Conclusion

Outbreaks of carbapenem-resistant *A. baumannii* are increasingly reported in many countries, including Taiwan, since 2005. They are sustained by clusters of similar strains that spread successfully intra-hospitals and inter-hospitals. Though there is some controversy about the existence of an epidemic clone throughout Taiwan, local spread of isolates should play an important role in increasing carbapenem-resistant *A. baumannii*. The finding of resistant gene determinants has not explained well the phenotypic variation in antimicrobial susceptibility. The gaps from resistant genes to phenotypic dynamics would be solved by functional genomic studies via the products of genome using high throughput analytic technologies.

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# 碳青黴烯類抗藥性鮑氏不動桿菌在台灣之現況

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**鮑氏不動桿菌(*Acinetobacter baumannii*)由於易對抗生素產生抗藥性，故常導致院內感染的暴發，最近已成爲院內感染主要病原之一。碳青黴烯類抗生素(carbapenem)已被廣泛用於治療多重抗藥性鮑氏不動桿菌造成之感染。然而，在台灣和其他許多國家都發現對碳青黴烯類抗生素具抗藥性鮑氏不動桿菌之分離率正逐年上升。這些對碳青黴烯類抗生素具抗藥性之鮑氏不動桿菌之散播已被證實主要經醫院內部或跨院間之菌株傳播而來；且經證實其抗藥性的產生主要是獲得一段苯唑西林水解β內酰胺酶(oxacillin-hydrolyzing-β-lactamase)(OXA)基因。此外在台灣各地區所分離出之亞胺培南(imipenem)抗藥性鮑氏不動桿菌經證明其帶有不同的抗藥基因。由此可推測鮑氏不動桿菌對亞胺培南之抗藥機制並非由單一基因所調控。隨著高通量基因組分析技術的進步，或許未來更多有關於鮑氏不動桿菌功能基因組的研究能幫助我們找出所有與其抗藥性相關的基因。**

***關鍵詞：碳青黴烯類抗生素、鮑氏不動桿菌、苯唑西林水解β內酰胺酶***

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