Carbapenem-resistant or Multidrug-resistant Acinetobacter Baumannii - a Clinician's Perspective

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Introduction

Acinetobacter baumannii has emerged as one of the most troublesome pathogens in the healthcare setting both globally and locally. Its remarkable ability to develop or acquire multiple antibiotic resistance and propensity to survive for prolonged periods under a wide range of environmental conditions, make it a frequent cause of hospital outbreaks and an endemic healthcare associated pathogen. It commonly targets the most vulnerable hospitalised and critically ill patients with breaches in skin integrity who require airway protection, causing pneumonia, urinary tract infection, wound infection and bacteremia.

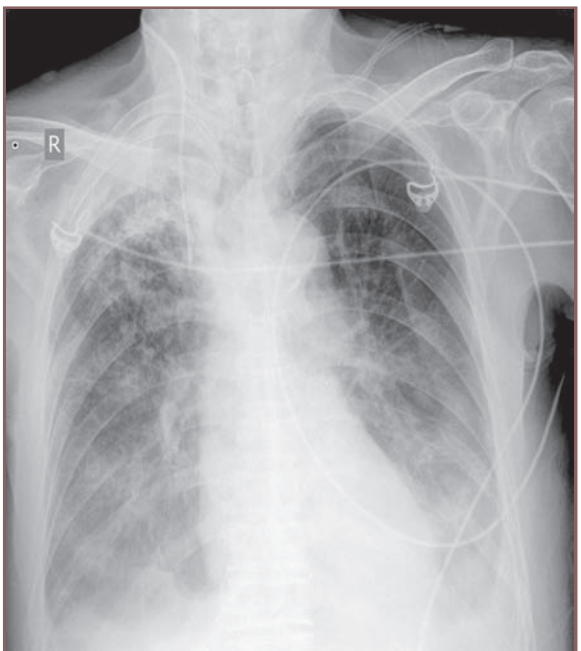

Figure 1. Chest radiograph of a patient with severe CRAB associated pneumonia and bacteremia

An Illustrative Case

A 44 year-old man was admitted to the medical ward for persistent fever and cervical lymphadenopathy. He subsequently developed bilateral pleural effusion and ascites. The diagnosis of Castleman's disease was confirmed by lymph node biopsy and chemotherapy was duly started. However, this was complicated by severe pneumonia resulting in respiratory failure, acute renal failure and septic shock (Figure 1). He was intubated and put on mechanical ventilation in the intensive care unit. Intravenous meropenem was started as empirical therapy with no apparent response. Two days later, his blood and sputum cultures yielded the same carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolate, which was resistant to meropenem and all other tested antibiotics in vitro except amikacin, tigecycline and colistin. After the culture and antibiotic susceptibility profile were reported, the treatment was changed to intravenous colistin. Unfortunately, the patient continued to deteriorate and succumbed 3 days later.

Confusion Over Multidrug Resistance

In the literature, various definitions have been used to describe the term multidrug-resistant A. baumannii (MDR-AB)[1]. Besides causing confusion among clinicians, the diversity of definitions makes it difficult to appreciate how the relative burden of antibiotic resistance in this pathogen differs in different countries. In Hong Kong, the Hospital Authority (HA) currently defines MDR-AB as A. baumanii that are concomitantly resistant to all the agents of four antibiotic classes (fluoroquinolones, aminoglycosides, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations) 2. Resistance to carbapenems is not considered in the definition. This means an isolate must be resistant to all of the following 13 antibiotics: ciprofloxacin, levofloxacin, gentamicin, netilmicin, amikacin, ceftriaxone, cefotaxime, ceftazidime, cefepime, ampicillin-sulbactam, cefoperazone-sulbactam, ticarcillin-clavulanate and piperacillin-tazobactam, before it is counted as an "MDR-AB". Thus, an isolate resistant to everything except amikacin would not be classified as an MDR-AB by the HA. Likewise, if there is a single "intermediate" susceptibility to any one of the 13 antibiotics, the isolate would also not be regarded as an "MDR-AB". Following through this line of thought, the patient mentioned in the case above will not be reflected to have suffered from an MDR-AB infection in the official statistics as shown in Table 1. Clearly, the operational definition adopted by the HA fails to consider the clinical relevance of the antibiotic

resistance profile and its potential impact on patient outcome. Unsurprisingly, this has previously caused and still continues to cause considerable confusion to clinicians and their subsequent management of affected patients.

Table 1. Multi-drug resistant organisms isolated in the hospitals under the Hospital Authority in 2009

MDRO	Specimen numbers	Numbers of MDROs isolated	MDRO rate
VRE	14,942	28	0.19%
ESBL	103942	20788 to 25985	20% to 25%
CRE	103942	51	0.05%
CRAB	8007	3122	39%
MDRA	8007	320	4%
CRPA	19820	941	4.75%
MRPA	19820	15	0.08%

MDRO, multidrug-resistant organism; VRE, vancomycin-resistant *Enterococcus*; ESBL, extended spectrum beta-lactamase; CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *A. baumannii*; MDRA, multi-drug resistant *Acinetobacter*; CRPA, carbapenem-resistant *P. aeruginosa*; MRPA, multi-drug resistant *P. aeruginosa*

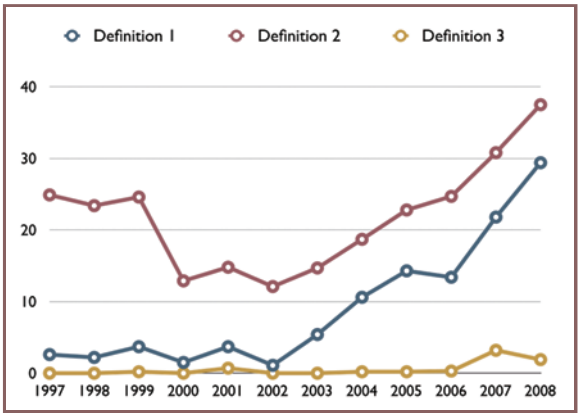

Figure 2. Changes in the multidrug-resistant (MDR) rate according to three different definitions, 1997-2008
Three approaches were used to define MDR-AB[3]:
1.Resistant to carbapenem class (imipenem and meropenem);
2.Resistance to representative agents from at least three antibiotic classes, including aminoglycosides, antipseudomonal penicillins, carbapenems, cephalosporins and fluoroquinolones;
3.Resistant to all agents or with exception of amikacin

Recently, a study assessed the trends in the resistance profile of *A. baumannii* in Hong Kong over a 12-year period (1997-2008) by using three different definitions and three proxy measures (multidrug resistance rate, cumulative incidence and incidence density) (Figure 2)[3]. The three definitions were used to represent the two ends and the middle of the spectrum of terminology adopted in the published literature[1]. The results showed that observations on secular changes for multidrug resistance in *A. baumannii* ranged from no significant changes to marked increases. It was concluded that the carbapenem class approach performs best[3]. Firstly, this single antibiotic class approach is currently being used for many established multidrug-resistant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Staphylococcus aureus (VRSA), vancomycin-resistant Enterococci (VRE) and carbapenem-resistant Enterobacteriaceae (CRE). Secondly, the carbapenem class is the drug of choice for serious infections caused by *A. baumanni* infections caused by carbapenem-susceptible strains. Thirdly, CRAB infections are commonly associated with the spread of OXA type carbapenemases, which cause extensive cross resistance to other beta-lactam antibiotics. Thus, it was suggested that this time-honoured "resistance to a critically important antibiotic class" approach be applied to monitor secular changes in the antibiotic resistance of *A. baumannii*. This approach would also be more relevant and practicable to clinicians.

Epidemiology and Clinical Outcomes of CRAB Infections

For many years, the carbapenem class has been considered as the drug of choice to treat serious *A. baumannii* infections. Until recently, the majority of clinical *A. baumannii* isolates had been sensitive to the carbapenems. As illustrated by the above case, a patient's culture and sensitivity results are usually not available to guide clinical decision until two to three days later. As a result, critically ill patients are routinely treated with empirical broad-spectrum antibiotics which target the most commonly encountered pathogens. Unsurprisingly, CRAB coverage hence becomes an issue of "hit-and-miss" in these scenarios. In life-threatening infections, broad-spectrum coverage before the infecting organisms are identified is essential because delay in institution of effective therapy within the initial 24 to 48 hours is well recognised to cause poor outcomes[4-5]. Carbapenems are used in such critical clinical scenarios because it is active against many community- and hospital-acquired pathogens, including extended-spectrum beta-lactamases (ESBL)-producing bacteria. Other advantages include favourable pharmacokinetic and pharmacodynamic properties, good safety profile and extensive clinical experience.

Unfortunately, the rapidly escalating prevalence of CRAB in many parts of the world in the past few years has undermined the reliability of the carbapenem class. To a large extent, the emergence of CRAB was attributed to the horizontal spread of the OXA type of carbapenemase genes (such as OXA-23) to highly successful clones of *A. baumannii*. Besides having resistance to almost all the beta-lactams, these OXA-23 positive bacterial clones are often resistant to the other antibiotics including fluoroquinolones, aminoglycosides and cotrimoxazole[6-9]. A recent study in Hong Kong reported that the annual CRAB rate has increased from 2.6% in 1997 to 29.4% in 20083. As in other parts of the world, the emergence of CRAB involves clonal spread. Strains with the OXA-23 genes were highly resistant to the carbapenems. In terms of clinical impact, CRAB infections are clearly associated with increases in both the length of hospital stay and mortality particularly in ventilator-associated pneumonia (VAP) and bloodstream infections[9-10]. A study by Sheng WH et al. demonstrated a higher mortality rate in patients with CRAB bacteremia than patients with carbapenem-sensitive *A. baumannii* bacteremia (46% vs. 28.3)[11]. We have reviewed 34 patients with CRAB infections in a local hospital (Table 2). The crude in-patient hospital mortality rate was 64%. Patients with blood stream infection and pneumonia had the highest mortalities; being 80% and 75%, respectively. While these infections are virtually untreatable, only 5 out of the 34 carbapenem and multidrug-resistant isolates were classified as "MDR-AB" by the HA's operational definition.

Table 2. Clinical outcomes of carbapenem-resistant Acinetobacter baumannii infections by infections sites

Site of Infections	Number of patients	Number of Death (%)
Blood	5	4 (80%)
Chest	16	12 (75%)
Intra-abdomen	8	5 (62.5%)
Wound	3	0 (0%)
Urine	2	1 (50%)
Overall	34	22 (64%)

Treatment of CRAB

At present, the therapeutic options for infections caused by antibiotic-resistant strains of *A. baumanni* are limited (Table 3). Tigecycline is a minocycline derivative with enhanced in-vitro activity against both Gram-positive and Gram-negative bacteria including *A. baumannii*. However, clinical data in treating *A. baumannii* infections remain limited. Breakthrough bacteremia by A. baumannii in patients receiving tigecycline has also been reported[12]. It is important to note that the emergence of tigecycline resistance may occur while the patient is on treatment[13]. Discrepancy in susceptibility results of tigecycline against *Acinetobacter* spp. due to different methods of testing causes considerable confusion that further hinders its clinical use in *Acinetobacter* infections. Unlike other beta-lactamase inhibitors, sulbactam possesses intrinsic bactericidal activity against *A. baumannii* isolates. Sulbactam containing regimens appear to have equivalent efficacy to other regimens when the isolates are susceptible to sulbactam[14]. However, the optimal dosage of sulbactam alone to treat serious *A. baumannii* is unknown.

Limited therapeutic options due to the slow pace of new antibiotic development against highly resistant strains of these pathogens have led to the reconsideration of the therapeutic role of colistin. Colistin, also known as polymyxin E, exerts its antibacterial effect by disturbing the bacterial cell membrane, thus increasing permeability, and eventual cell death. Colistin has retained activity against many multiple drug resistant gram-negative pathogens including *P. aeruginosa* and *A. baumannii*. Though the drug was discovered over 50 years ago, high quality pharmacokinetic data are lacking. Clinical outcomes vary for different types of infections. In general, patients with pneumonia were found to have a low response rate (25%)[15]. The poor performance in pneumonia may be explained by poor penetration into the lung. It was demonstrated that the efficacy of colistin in reducing the bacterial burden was poor in a murine model of pneumonia caused by *A. baumannii*[16]. It has been suggested that increased dosage or coadministration of nebulised colistin may increase the response rate. However, higher dosage may increase the risk of side effects such as nephrotoxicity and neurotoxicity. Recently, a randomised controlled study demonstrated no beneficial effects on clinical outcomes of adjunctive nebulised colistin for therapy of Gram negative bacteria associated ventilator-associated pneumonia[17]. Renal toxicity is of particular concern in patients with a history of renal impairment, the elderly, and those given concomitant nephrotoxic drugs. However, nephrotoxicity rates are now lower than those previously reported in the 1970s. Dosing should be adjusted in patients with preexisting renal impairment.

Conclusion

A. baumannii is emerging as an opportunistic gram-negative pathogen that targets vulnerable hospitalised patients causes a range of nosocomial infections and that also displays ever-increasing resistance worldwide. Nowadays, it seems that we are losing the antibiotics which can target these highly resistant organisms. Furthermore, the inconsistencies in defining multidrug resistance in this pathogen have caused considerable confusion to both clinicians and researchers. One way to circumvent this is to replace the ill-defined term MDR-AB with CRAB in surveillance programmes. Patients with CRAB infections are clearly associated with high mortality and increased hospital cost which highlights the urgent need for novel strategies in preventing further highly-resistant bacteria emergence, and perhaps a collective approach in facing, addressing and tackling the problem head-on may be the most effective measure in curtailing this threat for the benefit of both our patients and healthcare workers alike.

Table 3. Antibiotics for the treatment of serious Acinetobacter infections

Antibiotics	Clinical Efficacy	Tissue distribution	Toxicity	Comments
Intravenous carbapenems (imipenem, meropenem, doripenem)	Excellent	Widely distributed including lung and CNS*	Increase seizure	It cannot be used in CRAB infections
Intravenous tigecycline	Limited clinical data Not recommended in bacteremia	Low serum level achieved due to rapid distribution of tigecycline into tissue and body fluids	Nausea and vomiting	U.S. FDA warning: increased risk of morality used to treat serious infections, particularly VAP, complicated skin and soft tissue infections and complicated intra-abdominal infections
Intravenous Colistin	Limited clinical data Poor outcomes in pneumonia and bacteremia	Poor lung penetration	Nephrotoxicity & neurotoxicity	Emergence of colistin resistance and associated with colistin use[18]
Intravenous sulbactam	Sulbactam-containing regimens have comparable efficacy to other regimens[14]	Widely disturbed except CNS	Well tolerate	Commercially available as combination with ampicillin (unasyn) and cefoperazone (sulperazon) in Hong Kong
Aminoglycosides	Seldom used as monotherapy	Poor lung and CNS penetration	Nephrotoxicity, ototoxicity, neuromuscular blockade	Aminoglycosdes and colistin have similar risk of nephrotoxicity[19]

CNS, central nervous system; CRAB, carbapenem-resistant A. baumannii; FDA, Food and Drug Administration; VAP, ventilator associated pneumonia

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