

MINIREVIEW

Global Challenge of Multidrug-Resistant *Acinetobacter baumannii*[▽]

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We may soon be facing the end of the “antibiotic era.” The initial and seemingly unstoppable success of antibiotics, the fruit of human ingenuity, has been countered by an escalation of resistance mechanisms in bacteria. This crisis has been described as an “unwinnable war” (www.wellcome.org). The statistics compiled as a result of surveillance efforts illustrate the emergence of many genera of bacteria that are resistant to all antibiotics (57, 60). The genus *Acinetobacter* epitomizes this trend and deserves close attention. *Acinetobacter* spp. display mechanisms of resistance to all existing antibiotic classes as well as a prodigious capacity to acquire new determinants of resistance (7). The increasing recovery in the clinic of multidrug-resistant (MDR) *Acinetobacter baumannii* is a frightening reality (112). This review summarizes the worldwide emergence of antibiotic-resistant *A. baumannii* as a nosocomial pathogen and focuses on its mechanisms of resistance against selected antibiotics. It concludes with a summary of current strategies in the treatment of MDR *A. baumannii* and offers perspectives on the control of this global public health threat.

GLOBAL EPIDEMIOLOGY

A. baumannii is a nonfermentative, gram-negative, nonmotile, oxidase-negative bacillus, whose natural reservoir still remains to be determined. Nevertheless, it is found in many health care environments and is a very effective human colonizer in the hospital (www.cdc.gov). The combination of its environmental resilience and its wide range of resistance determinants renders it a successful nosocomial pathogen (137). As such, *A. baumannii* is emerging as a cause of numerous global outbreaks (213), displaying ever-increasing rates of resistance (Tables 1 and 2; Fig. 1). There are reports of MDR *A. baumannii* from hospitals in Europe, North America, Argentina, Brazil, China, Taiwan, Hong Kong, Japan, and Korea and from areas as remote as Tahiti in the South Pacific (6, 70, 99, 105, 111, 132, 136, 157, 209, 232). These MDR strains often spread to cause outbreaks throughout entire cities, countries, and continents (6, 32, 95, 208). The importation of MDR strains from areas with high rates of antimicrobial resistance to

areas with historically low rates, such as from Spain to Norway, has been demonstrated (139). More recently, cases of United Kingdom and U.S. military and nonmilitary personnel returning from operations in Iraq and Afghanistan and harboring infections caused by MDR *A. baumannii* are receiving increased attention (33, 63, 74, 81, 203).

INFECTIONS DUE TO *A. BAUMANNII*

MDR *A. baumannii* infections tend to occur in immunosuppressed patients, in patients with serious underlying diseases, and in those subjected to invasive procedures and treated with broad-spectrum antibiotics (54). Thus, infections due to *A. baumannii* are frequently found in intensive care units (ICUs), where they are implicated as the cause of ventilator-associated pneumonia (VAP), urinary tract infections, and bacteremia. *A. baumannii* also causes, albeit less frequently, complicated skin and soft tissue, abdominal, and central nervous system infections (46). Of recent importance is that *A. baumannii* has become a major pathogen found in combat-associated wounds (2). The factors contributing to colonization, virulence, and invasion are being defined (187).

It is often difficult to distinguish between infection and colonization with *A. baumannii* (79). There is considerable controversy over whether infections caused by this organism lead to unfavorable outcomes (9, 41, 55). However, it is believed by some clinicians that the recovery of *A. baumannii* in the hospitalized patient is an indicator of severe illness, with an associated mortality of approximately 30% (225). Case series of *A. baumannii*-causing infections in community dwellers are detailed. An occurrence of community-acquired pneumonia associated with high mortality in patients in northern Australia and southern Asia was recently described. A significant percentage of the patients in that study were bacteremic (31.6%) and had acute respiratory distress syndrome and disseminated intravascular coagulation (23, 102, 177). These clinical vignettes raise the possibility that some isolates may have acquired virulence factors that are normally not found in the majority of *Acinetobacter* spp.

GENETIC BASIS OF ANTIBIOTIC RESISTANCE

Acinetobacter spp. (and *A. baumannii* in particular) have become resistant to many classes of antibiotics. Firstly, *Acinetobacter* spp. appear to be well suited for genetic exchange and

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TABLE 1. Survey of global susceptibility of *A. baumannii* to selected antibiotics

Geographic area	Location/study ^a	Yr	Susceptibility (%) to ^b :										Reference
			FEP	CAZ	CIP	GEN	IMP	LVX	SAM	MEM	TZP	SXT	
North America	SENTRY	2001–2004	57	54	54		89		71	84			50
	United States (hospital isolates)/SENTRY	1998–2003	63	62	61	64	93				63		172
	United States (hospital isolates)/MYSTIC	2003	63	64	59	63	92	60		87	61		162
	United States (non-ICUs)	2001	47	45	35	44	93	45		85	58		87
	United States (ICUs)	2001	56	49	45	53	96	54		91			87
	United States (ICUs)/SENTRY	2001	51	57	53	53	81			79	59		191
	United States (ICUs)/TSN	2000–2002	44	42	40	47	87	44		66	54	51	83
	Canada (ICUs)/TSN	2000–2002	67	71	72	73	96	61		94	71	75	83
	United States/ICUSS	2000	66	55	43		95		78		79		48
Europe	SENTRY	2001–2004	44	40	39		74		48	70			50
	Italy (ICUs)/TSN	2000–2002	18	26	21	23	78	14		75	35	44	83
	France (ICUs)/TSN	2000–2002	28	35	38	49	94			68	75	45	83
	Germany (ICUs)/TSN	2000–2002	74	67	75	82	96	82		96	82	84	83
	Sweden (ICUs)	1999–2000			89		96				40	96	62
	Spain (hospital isolates)	2001	49	24	7	15	60	10	58	49	17	32	147
	United Kingdom and Ireland (bacteremia)	2001–2002		35	79	83	100				87		161
	Italy (respiratory isolates)	1997–1999	55	42	48	54	87			84	49	57	40
Asia/Pacific	SENTRY	2001–2004	58	58	55		74		59	73			50
	Korea (hospital isolates)	2003	59	45	42	36	87		53	75	58	43	100
	China (ICUs)	2002	70	65	66		92		80		70		220
	Japan (hospital isolates)	2002	85	89			95		97				76
	Taiwan (hospital isolates)/TSAR	2000	40	27	31	18	98				26	22	97
Latin America	SENTRY	2001–2004	36	32	35		86		52	84			50
	Brazil/SENTRY	2001	37	29	33	39	98	33		97	31	37	83
	Argentina (hospital isolates)	2001–2002	37	23			85	17	32		22		19

^a SENTRY, SENTRY Antimicrobial Surveillance Program; MYSTIC, Meropenem Yearly Susceptibility Test Information Collection; TSAR, Taiwan Surveillance of Antimicrobial Resistance; ICUSS, Intensive Care Unit Surveillance System; TSN, The Surveillance Network; TSAR, The Taiwan Surveillance of Antimicrobial Resistance Program.

^b FEP, cefepime; CAZ, ceftazidime; CIP, ciprofloxacin; GEN, gentamicin; IMP, imipenem; LVX, levofloxacin; SAM, ampicillin-sulbactam; MEM, meropenem; TZP, piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole.

are among a unique class of gram-negative bacteria that are described as “naturally transformable” (115, 121). *Acinetobacter baylyi* strain ADP1, for instance, displays a remarkable capacity for natural competence, being up to 100 times as competent as calcium chloride-treated *Escherichia coli* (121). ADP1 also readily demonstrates homologous recombination. *Acinetobacter* strains lacking *mutS* (part of the mismatch repair system that preserves genomic stability) exhibit increased mutation rates (231). The presence of competence genes *comFECB* and *comQLONM* allows the ready uptake of DNA from

the environment (5, 18, 66, 110, 154). To date, it is unknown whether other species of *Acinetobacter* (such as *A. baumannii*) are naturally competent or whether environmental conditions can be altered to facilitate pathogenicity or antibiotic resistance gene acquisition.

A recent study describing the genome sequences of both susceptible (SDF) and resistant (AYE) isolates of *A. baumannii* has shed light on the abundance of resistance genes found in this organism (47). Fournier et al. (47) identified an 86-kb region called the AbaR1 resistance island in AYE that contained a cluster of 45 resistance genes in the MDR isolate. Among the key resistance genes identified were those coding for VEB-1, AmpC, and OXA-10 beta-lactamases, various aminoglycoside-modifying enzymes (AMEs), and tetracycline efflux pumps. Detailed genetic analysis of AbaR1 showed that it was also composed of mobile genetic elements (transposons) and other genes previously identified in *Pseudomonas* spp., *Salmonella* spp., and *E. coli*. The distribution of this large resistance island among other isolates of MDR *A. baumannii* still remains to be determined. The homologous location in the susceptible strain of *A. baumannii* (SDF) that was sequenced consisted of a 20-kb genomic island devoid of resistance genes.

Another contemporary paper describes the sequence analysis of the *A. baumannii* ATCC 17978 genome (187). The au-

TABLE 2. Meropenem resistance in *Acinetobacter baumannii*^a

Yr	No. of isolates	% of isolates that were:		
		Susceptible	Intermediate	Resistant
1998	171	84.8	9.4	5.9
1999	123	89.4	2.4	8.1
2000	309	76.4	4.5	19.1
2001	376	77.4	1.1	21.5
2002	437	72.5	4.4	23.1
2003	366	81.7	3.8	14.5
2004	554	75.3	6.1	18.6
2005	357	64.4	7.0	28.6

^a Data were collected from the MYSTIC website (www.mystic-data.org).

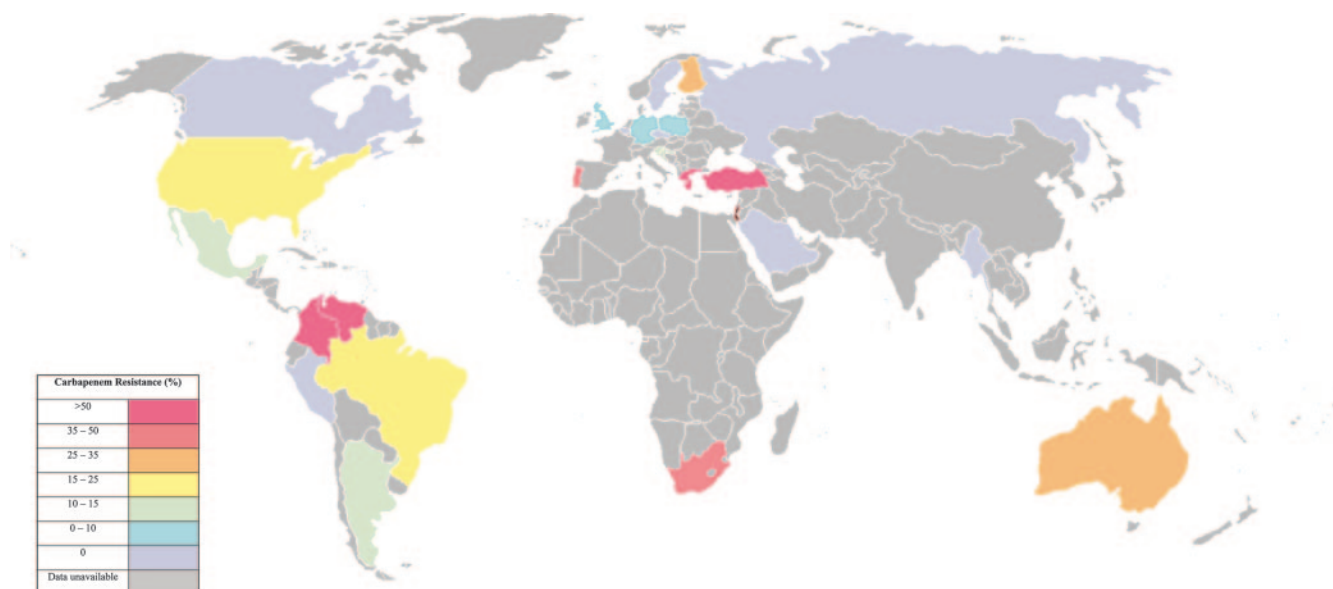


FIG. 1. *Acinetobacter* isolates resistant to carbapenems (Meropenem Yearly Susceptibility Test Information Collection [MYSTIC], 2004). Data were extracted from the MYSTIC database (www.mystic-data.org).

thors combined sequencing and insertional mutagenesis with *Caenorhabditis elegans* virulence assays and developed a new pathogenicity assay using *Dictyostelium discoideum*. It was found that the assembled genome from an isolate dating to 1951 contained 3.98 million base pairs and had 3,830 open reading frames (148). A significant fraction (nearly 17%) of the open reading frames were located in 28 putative alien islands, indicating that the genome acquired a large amount of foreign DNA. Surprisingly, it was also found that a large number of genes contained virulence islands, suggesting that the organism devotes a considerable portion of its genome to pathogenesis. The largest virulence island contained genetic elements homologous to the type IV secretion systems of *Legionella* and *Coxiella burnetii*. By using insertional mutagenesis, the virulence properties of six of these alien islands were confirmed in *C. elegans*.

An insertional sequence similar to one described by Fournier et al. (47) was also detected. This resistance island was 13,277 base pairs in length, was comprised of nine genes, and was located between the 5' and 3' ends of the putative ATPase gene. Interestingly, only one drug resistance gene, *sulI*, was found in this insertional "hot spot." Smith et al. (187) commented that the *A. baumannii* ATCC 17978 isolate possesses an additional 74 potential drug resistance genes, including 32 efflux pump genes, 11 permease genes, and also 26 genes encoding resistance to heavy metals. These findings imply that the designated "hot spot" is not the only location in which genes have inserted into this organism. Since the full sequences of the two French isolates are not yet available, a comparison of resistance and pathogenicity islands cannot yet be made.

Mobile genetic elements and insertion sequences. More than 25 years ago it was demonstrated that *Acinetobacter* spp. can acquire antimicrobial resistance factors through conjugation of plasmids (59, 127). Currently, transposons (mobile genetic elements that are integrated into the chromosome or carried on plasmids) are known to be important in the dissemination

of genetic determinants of resistance in *Acinetobacter* spp. (34, 142). Many of these transposons contain integrons (predominantly class 1). Integrons are genetic elements that, although unable to move themselves (for this they need to be carried on a plasmid or a transposon), contain an *int* gene and gene cassettes that can be mobilized to other integrons or to secondary sites in the bacterial genome (150, 182, 204). As in other gram-negative bacteria, an MDR phenotype in *A. baumannii* results when integron-borne resistance determinants against different classes of antibiotics coexist, giving rise to MDR gene cassettes. The selection and dissemination of the mobile elements carrying these resistance genes may be amplified in the clinical setting by the indiscriminate use of antibiotics (183, 223). The description of insertion sequences (ISs) that promote gene expression has also played an important role in explaining the regulation of resistance. To illustrate, the presence of the IS_{Aba1} element, which has been identified in *A. baumannii* but not in *Enterobacteriaceae* or in *Pseudomonas aeruginosa* (181), results in overexpression of AmpC and OXA-51/OXA-69-like beta-lactamases and in decreased levels of susceptibility to ceftazidime and carbapenems, respectively (65, 205).

MECHANISMS OF RESISTANCE TO SELECTED ANTIBIOTICS

Resistance to beta-lactams. The mechanisms underlying resistance to beta-lactams in *A. baumannii* are (i) their hydrolysis by beta-lactamases, (ii) changes in penicillin-binding proteins (PBPs) that prevent their action, (iii) alterations in the structure and number of porin proteins that result in decreased permeability to antibiotics through the outer membrane of the bacterial cell, and (iv) the activity of efflux pumps that further decrease the concentration of antibiotic within the bacterial cell.

(i) **Class A beta-lactamases.** Although TEM-1 beta-lactamase is known to occur in *A. baumannii*, class A extended-

spectrum beta-lactamases (ESBLs) have been found only more recently (210). *A. baumannii* strains harboring PER-1, an ESBL, demonstrate high-level resistance to penicillins and extended-spectrum cephalosporins (ceftazidime minimum inhibitory concentration [MIC], 256 µg/ml; cefepime MIC, 32 µg/ml), but fortunately, PER-1 beta-lactamase does not confer resistance to carbapenems in *A. baumannii*. PER-1 is very prevalent among *A. baumannii* strains in Turkey and Korea (93, 229) and has also been reported in this organism in France, Belgium, and Bolivia (20, 130, 150). A recent molecular and epidemiological analysis described PER-1 for the first time in the United States (74).

A. baumannii harboring the integron-borne VEB-1, also an ESBL, has caused outbreaks in French and Belgian hospitals (130, 131, 151). In China, *A. baumannii* producing SHV-12 ESBL was reported (71). In addition, a report of SHV-12 and TEM-116 in *A. baumannii* from The Netherlands was published (134). Endimiani and colleagues have found the TEM-92 ESBL in isolates of *A. baumannii* in Italy (39).

CTX-M-2, an ESBL characterized by enhanced hydrolysis of cefotaxime and ceftriaxone, was found in epidemic strains of *A. baumannii* in a neurosurgical ward in Japan, as well as in strains of *A. baumannii* isolated in Bolivia (20, 133). Interestingly, the dissemination of the *bla*_{CTX-M} gene seems not to be as widespread in this organism as among *Enterobacteriaceae*.

Since the clinical detection of ESBLs in *A. baumannii* is not standardized and is complicated by the presence of chromosomal cephalosporinases, it is uncertain to what extent class A ESBLs are distributed in *A. baumannii*. In our experience, many clinical isolates of *A. baumannii* test resistant to ceftazidime and cefepime. In *Enterobacter* spp. and *Klebsiella pneumoniae*, the class A ESBLs in an AmpC background are associated with clinical failure when cefepime is used for treatment despite in vitro susceptibility to that agent (143, 198).

(ii) Class B beta-lactamases. The increase in the number of metallo-beta-lactamases (MBLs) in *A. baumannii* is an ominous development in the global emergence of resistance to beta-lactams (216). MBLs are class B beta-lactamases that are able to hydrolyze carbapenems as well as every other beta-lactam antibiotic with the exception of aztreonam. They differ from class A and D carbapenemases by having a metal ion in the active site, usually zinc, which participates in catalysis (216, 217).

IMP MBLs were first described in a strain of *P. aeruginosa* found in Japan in 1988 (222). Mirroring the spread of other beta-lactamases, IMP MBLs are now found around the world in different genera. In *A. baumannii* IMP MBLs are usually detected as part of a class 1 integron, as first discovered in the Far East. Although MBLs are not the predominant carbapenemases in *A. baumannii*, several have been described: IMP-1, IMP-2, IMP-4, IMP-5, IMP-6, and IMP-11 (216, 217). One of the early-described MBLs in *A. baumannii* in England was traced to an infected patient from Spain (206). The presence of several types of IMP beta-lactamases in *A. baumannii* from Japan has been reported (136), but it was in Hong Kong where they seemed to have first appeared (27). Carbapenem resistance mediated by IMP-type MBLs is now a grave problem in Korea and in Pacific rim nations (99). In the Americas, the only report of an MBL in *A. baumannii* is that of an IMP-producing isolate from Brazil (52, 200). Verona integron-encoded MBL (VIM-1) was first identified in Italy in 1997 in a *P.*

TABLE 3. OXA carbapenemases in *Acinetobacter baumannii*

Carbapenemase type	OXA carbapenemases
Acquired	
Chromosomal	OXA-24, OXA-25, OXA-26, OXA-40, OXA-58 ^a
Plasmid	OXA-23, OXA-58 ^a
Naturally occurring	
OXA-51/69 like	OXA-64, OXA-65, OXA-66, OXA-68, OXA-70, OXA-71, OXA-78, OXA-79, OXA-80, OXA-82

^a OXA-58 has been described both as chromosomal and as a plasmid-mediated carbapenemase in *A. baumannii*. Data are from references 17 and 152.

aeruginosa isolate (98); *A. baumannii* harboring VIM-2 has been reported only in Korea (233).

The diversity of MBLs in *A. baumannii* isolates from Korea is highlighted by the recent description of a Seoul imipenemase (SIM-1), a novel MBL (101). SIM-1 is a member of the B1 subclass. The broad-spectrum SIM-1 MBL possesses 69% identity with IMP-12 MBL and 64% identity with IMP-9 MBL. There is intriguing genetic evidence to suggest that the *bla*_{SIM-1} cassette may have originated from the *Pseudomonas alcaligenes* In55044 superintegron (101).

(iii) Class C beta-lactamases. *Acinetobacter* spp., like other gram-negative organisms, have a chromosomally encoded class C beta-lactamase. Recent phylogenetic analysis found that chromosomal *ampC* genes in *Acinetobacter* spp. likely descend from a common beta-lactamase gene ancestor and are more closely related to each other than to *ampC* genes present in other species of bacteria. It is proposed that these represent a distinct family of beta-lactamases, the *Acinetobacter*-derived cephalosporinases (ADCs) (73). The *bla* genes code for class C cephalosporinases that hydrolyze penicillins and narrow-spectrum and extended-spectrum cephalosporins, but not cefepime or carbapenems. Thus, many clinical isolates of *A. baumannii* are resistant to ceftazidime. Given the genetic diversity of *Acinetobacter* spp., it is likely that more variants of the ADCs will be found. To date, 28 *bla*_{ADC} genes have been found and are listed in GenBank.

(iv) Class D beta-lactamases. Class D OXA beta-lactamases are usually robust penicillinases (oxacillinases). Some OXAs (i.e., OXA ESBLs) are also able to hydrolyze extended-spectrum cephalosporins (4, 218). Most worrisome are OXA beta-lactamases that inactivate carbapenems. The first description of such an OXA carbapenemase in *A. baumannii* was OXA-23, which was obtained from a clinical isolate found in Scotland in 1985 before the introduction of carbapenems. Since then, this plasmid-encoded enzyme, initially named ARI-1 (*acinetobacter* resistant to imipenem) has been discovered in England, Brazil, Polynesia, Singapore, Korea, and China (17, 78). OXA-58, a plasmid-borne carbapenemase, was found in France, England, Argentina, Spain, Turkey, Romania, Austria, Greece, Scotland, and Kuwait (28, 119, 156). The significant contribution of these enzymes to carbapenem resistance in *A. baumannii* has been emphasized, particularly when they are accompanied by IS_{Aba1} and IS_{Aba3} in the naturally occurring plasmid (MICs for imipenem and meropenem, ≥32 µg/ml) (119).

The remainder of the carbapenem-hydrolyzing oxacillinases are thought to be chromosomally mediated enzymes (Table 3).

A contemporary genetic analysis has categorized the OXA carbapenemases into eight distinctive groups (218). Their widespread presence, although with enough differences to allow separation into distinct subgroups, may indicate that oxacillinases are also an essential component of the genetic makeup of *Acinetobacter* spp. (218). The outbreaks of *A. baumannii* harboring OXA-40 and OXA-58 in the United States reflect the dissemination and emergence of OXA enzymes in this organism in the Western hemisphere, raising their status as emerging carbapenemases (74, 114). OXA-51/69-like beta-lactamase deserves special mention as a “naturally occurring” chromosomal enzyme in *A. baumannii*; it has been found in isolates from four continents, and its expression varies according to the presence of *IS*_{Aba1}, as previously discussed (152). It is notable that the recent determination of the crystal structure of OXA-24 carbapenemase suggests a novel catalytic role for Tyr112 and Met223 side chains (178).

(v) Changes in OMPs and PBPs. Understanding the contribution of porins or outer membrane proteins (OMPs) to antibiotic resistance in *A. baumannii* has been a particular challenge. Unfortunately, it is difficult to accurately compare the loss of OMPs. Laboratory studies reveal that there is variability in the number of observed OMPs (31). A similar complex picture has emerged for PBPs (45).

The investigation of the epidemic of MDR *A. baumannii* in New York City demonstrated the presence of carbapenem-resistant isolates with reduced expression of 37-, 44-, and 47-kDa OMPs and increased expression of class C cephalosporinases (157), although in that report only a relatively small number of isolates were studied and MBL or OXA enzymes were not systematically investigated. Similarly, in isolates from Madrid, the loss of 22-kDa and 33-kDa OMPs combined with the production of OXA-24 resulted in resistance to carbapenems (13).

Recently, a 43-kDa protein in *A. baumannii* was identified as a homologue of OprD (a well-studied porin frequently associated with imipenem resistance in *P. aeruginosa*) (37). The channel formation of CarO, a 29-kDa OMP which confers resistance to both imipenem and meropenem in *A. baumannii*, has been well characterized (108, 129, 186).

The resistance of *A. baumannii* to carbapenems is also explained by reduced expression of PBP-2, as described for isolates from Seville, Spain (45). Of note, these strains had loss of OMPs and production of beta-lactamases, illustrating the interplay of several different mechanisms of resistance against one class of antibiotics. Establishing the relative contribution of the action of beta-lactamases, beta-lactam penetration through OMPs, and interaction with other mechanisms of resistance, and the control of their expression presents formidable challenges.

(vi) Efflux pumps. Efflux pumps exemplify a unique phenomenon in drug resistance: a single mechanism causing resistance against several different classes of antibiotics. These multicomponent pumps mediate the efflux of compounds toxic to the bacterial cell, including antibiotics, in a coupled exchange with protons. Distinct families of efflux pumps widely found in various species of bacteria have been identified: the major facilitator superfamily, the small multidrug resistance superfamily, the multidrug and toxic compound extrusion superfamily, and the resistance-nodulation-cell division family (153). In *A.*

baumannii, the AdeABC efflux pump, a member of the resistance-nodulation-cell division family, has been well characterized. It pumps aminoglycosides, cefotaxime, tetracyclines, erythromycin, chloramphenicol, trimethoprim, and fluoroquinolones (116). The overexpression of the AdeABC efflux pump may also confer high-level resistance to carbapenems (in conjunction with carbapenem-hydrolyzing oxacillinases) (119). A mechanism that controls the expression of this pump was elucidated as a two-step regulator (*adeR*) and sensor (*adeS*) system; in the *adeR* or *adeS* gene, a single point mutation results in increased expression and hence in increased efflux (118). Recently, AbeM, another multidrug efflux pump from *A. baumannii* has been identified and characterized as a member of the multidrug and toxic compound extrusion family. Its spectrum of antibiotic substrates appears to be limited to fluoroquinolones, among other toxic compounds (192).

Resistance to aminoglycosides. In addition to the above-described AdeABC multidrug efflux pump, resistance to aminoglycosides in *A. baumannii* is mediated principally by aminoglycoside-modifying enzymes (AMEs). These include aminoglycoside phosphotransferases, aminoglycoside acetyltransferases, and aminoglycoside nucleotidyltransferases. In a study performed by Nemec and coworkers, aminoglycoside-resistant isolates from 13 countries were analyzed for the genes encoding AMEs (135). PCR mapping revealed that *aphA1*, *aphA6*, *aacC1*, *aacC2*, *aacA4*, *aadA1*, and *aadB* were present in these isolates. A United States-based study showed that *aphA6*, *aadA1*, *aadB*, *aacC1*, and *aacC2* were present in the collection of isolates from Walter Reed Army Medical Center (74). Turton et al. examined isolates from military and civilian casualties from the Iraq conflict who were hospitalized in the United Kingdom and revealed *aacC1*, *aadA1a*, *aadB*, *aacA4*, and *aadA1* genes encoding AMEs (203).

Seward et al. further demonstrated that similar AMEs are found in unrelated isolates of *Acinetobacter* spp. and that particular genes are not restricted to specific areas of the world. Hence, similar integrons have been found in genotypically distinct isolates from different locations worldwide (183, 184). This finding has been confirmed in Spain, in England, and throughout Europe (53, 135, 204), where a remarkably stable class 1 integron with the same variable region is retrieved from isolates that are genotypically unrelated, indicating their importance in the dissemination of antibiotic resistance genes.

Recently, a new type of AME, encoded by *aac(6')-Iad*, has been discovered and found to play a central role in amikacin resistance among *Acinetobacter* spp. in Japan (36). To date, bifunctional AMEs that modify more than one class of aminoglycosides have not been described in *A. baumannii*, as they have been in *Serratia marcescens*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *P. aeruginosa* (91).

Resistance to quinolones. Resistance of *A. baumannii* to quinolones is often caused by modifications in the structure of DNA gyrase secondary to mutations in the quinolone resistance-determining regions of the *gyrA* and *parC* genes (185, 211, 212). These changes result in a lower affinity for the binding of the quinolone to the enzyme-DNA complex. As mentioned above, a second mechanism of resistance to the quinolones is mediated by efflux systems that decrease intracellular drug accumulation. It is unclear why some quinolones

(clinafloxacin, gatifloxacin, levofloxacin, trovafloxacin, gemifloxacin, and moxifloxacin) display slightly increased activity against *A. baumannii* compared to ciprofloxacin (64). Unlike in *Enterobacteriaceae*, plasmid-mediated quinolone resistance (*qnr* genes) or the gene encoding the AME with the capacity to modify ciprofloxacin has not yet been reported in *A. baumannii* (138, 165, 201, 202).

Resistance to tetracyclines. Two different mechanisms of resistance to tetracyclines have been widely described in *A. baumannii*. TetA and TetB are specific transposon-mediated efflux pumps; TetB determines the efflux of both tetracycline and minocycline, whereas TetA drives only the efflux of tetracycline (61, 75). The second mechanism is the ribosomal protection protein, which shields the ribosome from the action of tetracycline. The *tet(M)* gene encodes this protein, which serves to protect the ribosome from tetracycline, doxycycline, and minocycline. This ribosomal protection protein found in *A. baumannii* is 100% homologous to the Tet(M) protein of *S. aureus* (163). Neither efflux nor the ribosomal protector protein seems to interfere with the action of tigecycline, a representative of a new class of antibiotics, glycylcyclines, related to tetracyclines. However, tigecycline is a substrate for TetX (a plasmid-borne flavin-dependent monooxygenase), although this enzyme has not been found in clinical isolates of *A. baumannii* (125).

So far, tigecycline has demonstrated encouraging in vitro activity against most *A. baumannii* isolates from clinical collections around the globe (24, 68, 174, 175, 190, 215), but there have been reports of resistance. Among 42 carbapenem-resistant *A. baumannii* isolates from the recent outbreak in the Chicago area, 6 had a tigecycline MIC of $\geq 4 \mu\text{g/ml}$ (the tigecycline breakpoint is defined by the Food and Drug Administration [FDA] as $\geq 8 \mu\text{g/ml}$). It is important to keep in mind that the achievable serum concentration of tigecycline at normal dosing is $0.63 \pm 0.28 \mu\text{g/ml}$, a value below the FDA breakpoint (114). Hence, it is concerning that bloodstream infections caused by non-tigecycline-susceptible *A. baumannii* are reported; such resistance appears to be at least partly attributable to an efflux pump mechanism (144). A recent analysis by Ruzin et al. confirms the role of the AdeABC efflux pump as a mechanism of resistance to tigecycline (169). The overexpression of the *adeABC* locus correlated with a three-fold increase in MIC in strains of the *Acinetobacter calcoaceticus*-*A. baumannii* complex. As previously mentioned, this pump confers broad substrate specificity which includes tigecycline, gentamicin, levofloxacin, and chloramphenicol. Furthermore, the AdeRS two-component system, which regulates the expression of AdeABC, was disrupted by an insertion sequence, IS_{Aba1}, in the tigecycline-resistant strains, whereas it remained intact in tigecycline-susceptible strains (169).

Resistance to polymyxins. Polymyxin B and polymyxin E (colistin, intravenous colistimethate sodium) are peptide antibiotics first isolated in 1947 that have been increasingly used as a "last-resort" treatment of infections caused by MDR *A. baumannii*. Unfortunately, there have been reports of resistance to colistin in *A. baumannii* that have been met with great alarm (51, 160, 207). In 2001, Urban et al. reported a case of polymyxin B-resistant *A. baumannii* (207). Heteroresistance (subpopulations of genetically identical subclones that are more resistant than the original parent clone) is a particularly fright-

ening development that has been recently described for *A. baumannii* (107). The impact of heteroresistance will need to be evaluated and monitored in a prospective manner as clinicians begin to study outcomes in patients undergoing treatment with colistin. In addition to colistin, Pournaras et al. have described similar findings with regard to carbapenems (155). It will be interesting to compare the genetic basis of this phenomenon in *A. baumannii* with what is known for other bacteria (e.g., *S. aureus* [170]).

The mechanism of resistance to colistin likely resides in modifications in the lipopolysaccharide of *A. baumannii* (acidification, acylation, or presence of antigens that interfere with binding of the antibiotic to the cell membrane) (145). We fear that resistance to colistin will become more widespread as the use of polymyxins increases.

IMPLICATIONS FOR DIAGNOSIS AND TREATMENT

Treatment of infections caused by *A. baumannii* is guided foremost by in vitro antimicrobial susceptibility assays. Among these, the determination of MICs by broth microdilution and agar dilution and their comparison with predetermined resistance breakpoints has been considered the "gold standard." However, the prediction of resistance in *A. baumannii* based upon these assays may be less certain than for other bacteria. Gaps in the current knowledge of the clinical response and bacterial mechanisms of resistance to antimicrobials make the existing breakpoints imperfect (86). Furthermore, the reliability and comparability of different methods of susceptibility testing such as disc diffusion and broth microdilution have not been clearly reconciled for *A. baumannii*. The persistence of subtle growth beyond an obvious end point by broth microdilution is a major worry in the case of beta-lactams, which explains its poor concordance with the disc diffusion method (193). Disc diffusion susceptibility testing may not yield accurate results for colistin and for polymyxin B, due to their large molecular size and poor diffusion in agar (51, 196). Hence, we suggest that Etest results for colistin should be confirmed with broth microdilution, especially when MICs are in the range of 1 to 2 $\mu\text{g/ml}$ (3). Likewise, the breakpoint criterion that determines the susceptibility of *A. baumannii* to tigecycline may require revision to improve the correlation between disc diffusion and broth microdilution methods and the harmonization between European and American standards (82).

Among the antibiotics that are considered as agents against MDR *A. baumannii*, tigecycline has received significant attention. As stated above, tigecycline has shown excellent in vitro activity against multiple clinical isolates of *A. baumannii* (63, 82, 215). Doripenem, a novel carbapenem, also promises to be active against susceptible *A. baumannii* (49, 83, 84, 128, 164). In initial in vitro studies, doripenem was not effective against *A. baumannii* isolates producing *bla*_{OXA-23} or *bla*_{IMP-4} (128) or MBLs. In subsequent trials, the MIC₅₀ usually was 0.5 $\mu\text{g/ml}$ and the MIC₉₀ was 16 $\mu\text{g/ml}$, with 75.8% of isolates susceptible (MIC, $\leq 4 \mu\text{g/ml}$).

Combination therapy. (i) In vitro studies. Combination antibiotic therapy is a strategy often employed in the treatment of MDR *A. baumannii*. This approach attempts to achieve synergy, particularly against MDR strains (Table 4). To support this clinical practice, in vitro combinations of antibiotics have

TABLE 4. Combinations of antibiotics demonstrating enhanced activity against carbapenem-resistant *A. baumannii*

Study type	Antibiotic combination (reference[s])
In vitro.....	Meropenem + ampicillin-sulbactam (90, 92) Imipenem + ampicillin-sulbactam (26) Rifampin + ampicillin-sulbactam (197) Rifampin + polymyxin B (197, 230) Rifampin + colistin (69) Imipenem + polymyxin B + rifampin (230) Imipenem + polymyxin B (230) Cefepime + ampicillin-sulbactam (173)
Animal models.....	Meropenem + ampicillin-sulbactam (92) Imipenem + ampicillin-sulbactam (226) Imipenem + tobramycin (124) Imipenem + rifampin (124, 226) Rifampin + tobramycin or colistin (124) Rifampin + ampicillin-sulbactam (226)
Clinical experience.....	Rifampin + colistin (126, 146) Colistin + others ^a (88, 189)

^a Imipenem, meropenem, ampicillin-sulbactam, piperacillin-tazobactam, cefepime, quinolones, and aminoglycosides.

long been examined using checkerboard methods, time-to-kill assays, and Etests (12). In this section, we review existing studies that have influenced clinical practice.

Recent observations have shown that combinations of sulbactam with aminoglycosides, rifampin, and azithromycin have demonstrated synergy against imipenem-susceptible strains (1, 179). In contrast, there is little advantage to combinations of sulbactam with cephalosporins. Sulbactam has intrinsic activity against *A. baumannii* but does not seem to enhance the action of other beta-lactams (15, 67, 219). Other combinations (e.g., quinolones and beta-lactams or imipenem and aminoglycosides) are also synergistic against imipenem-susceptible strains (22, 85). Colistin combined with rifampin (or with meropenem and azithromycin) achieved synergy against some imipenem-susceptible isolates (58, 199). We speculate that the role of polymyxins in combination with other antibiotics allows the rapid permeabilization of the outer membrane, permitting the entry of other agents into the bacterial cell.

Either (i) polymyxin B combined with imipenem, (ii) imipenem plus rifampin, or (iii) the triple combination of polymyxin B, imipenem, and rifampin was synergistic when tested against imipenem-resistant strains from Queens, NY (MBL negative by Etest) (230). In contrast, similar combinations failed to demonstrate reliable synergy against strains from England harboring OXA-23 (221). Cefepime in combination with sulbactam or with aztreonam was synergistic or partially synergistic against a collection of carbapenem-resistant strains, as long as these were not MBL-producing strains (173, 176). Imipenem or meropenem, combined with ampicillin/sulbactam, was active against carbapenem-resistant strains and, in one instance, even against MBL-producing strains (26, 90, 92). The combinations of tigecycline with amikacin, meropenem, imipenem, quinolones, sulbactam, and rifampin were indifferent against carbapenem-resistant strains of *A. baumannii* (180). It must be recalled that the results of in vitro combinations may not guide and predict successful antibiotic therapy.

(ii) Animal models. Animal models of *A. baumannii* infection have served as a guide to test the efficacy of in vitro combination therapies. In surprising contrast to results obtained in vitro, the combination of imipenem and amikacin for the treatment of imipenem-susceptible *A. baumannii* strains in a guinea pig pneumonia model was less effective treatment than either antibiotic alone (8). Similarly, improvements in the bactericidal activity or mortality were not achieved with combinations of levofloxacin with amikacin, levofloxacin with imipenem, or imipenem with amikacin (80). A different pneumonia model with susceptible strains demonstrated synergy with the combination of doxycycline and amikacin but not with imipenem and amikacin (167).

In a mouse pneumonia model investigating carbapenem-resistant strains, the value of adding tobramycin to imipenem and combining rifampin with imipenem, tobramycin, or colistin was demonstrated. In contrast, the combination of imipenem and sulbactam was not effective (124). A different mouse pneumonia model, however, revealed that only the combination of imipenem and sulbactam or regimens containing rifampin had a true bactericidal effect (defined in that paper as ≥ 3 log kill) (226). Similarly, a model of intraperitoneal infection showed significantly higher survival with meropenem and sulbactam than with either antibiotic alone (92).

Rifampin has excellent efficacy in different animal models in combination with other antimicrobials. Its use as monotherapy in animal models, although effective, is limited by the potential emergence of resistance during treatment (141). In contrast to the in vitro studies cited above and clinical studies summarized below, colistin showed unexpectedly poor results, in both pneumonia and endocarditis models (123, 166).

Clinical experience. The observations in vitro and in animal models, although important, are not always applicable in clinical practice (158). Furthermore, the studies and case series that illustrate the experience with different antibiotics in the treatment of MDR *A. baumannii* are also difficult to interpret because of potential biases. Clinical trials with appropriately designed controls and random allocation of treatments serve as the necessary standard for the practitioner. Unfortunately, such prospective studies to guide combination antibiotic therapy of MDR *A. baumannii* have not been realized. In the discussion that follows, we review primarily the clinical experience with carbapenems, colistin, and tigecycline.

There are several studies that describe the experience with various single agents used in the therapy of infections with MDR *A. baumannii*. In a retrospective study of VAP caused by *A. baumannii* that was imipenem and sulbactam susceptible, outcomes with sulbactam were similar to those with imipenem as measured by survival, days of mechanical ventilation, and length of ICU stay (228). Other retrospective comparisons of sulbactam and imipenem for the treatment of bacteremia have shown similar results (25, 77). The adequate performance (cure rates of up to 67.5%) of sulbactam in the treatment of different types of infections, including meningitis, pneumonia, peritonitis, and surgical site and urinary tract infections, caused by MDR *A. baumannii* that was also resistant to imipenem was further confirmed by prospective and retrospective series of patients (104, 188).

Uncontrolled studies reporting the successful use of colistin in combination with other antimicrobials (i.e., meropenem,

imipenem, ampicillin/sulbactam, cefepime, aztreonam, piperacillin-tazobactam, quinolones, and aminoglycosides) for the treatment of infections with MDR *A. baumannii*, especially VAP, have been published, achieving loosely defined "favorable outcomes" in up to 76% of cases (88, 189). The combination of colistin with rifampin has also been successful in the treatment of small groups of patients with VAP, but this analysis was also retrospective and uncontrolled (126, 146). In a small study including only 10 patients followed prospectively, the combination of rifampin and carbapenem for the treatment of carbapenem-resistant *A. baumannii* VAP yielded unfavorable results, contradicting promising animal data (171).

In a prospective study, colistin was compared to imipenem for the treatment of VAP caused by imipenem-susceptible MDR *A. baumannii*. In-hospital and VAP-associated mortality and nephrotoxicity were similar in both groups (56). Likewise, a cohort of patients receiving colistin for infections caused by MDR *A. baumannii* and *P. aeruginosa* found similar efficacy and no instances of renal toxicity compared to patients receiving other antibiotics (159). Several retrospective case series have been published supporting the value of colistin for the treatment of MDR *A. baumannii*, including its use for bacteremia, orthopedic-device infections, osteomyelitis, and central nervous system infections (88, 89, 103, 122). The addition of nebulized colistin to parenteral therapy for the treatment of MDR *A. baumannii* pneumonia has been advanced as a way to overcome the limited penetration of systemic colistin into the lungs and minimize its potential nephrotoxicity. Although published experience with aerosolized colistin is favorable, it is based upon a retrospective uncontrolled study. Bronchospasm is an occasional side effect of this therapy (94, 109). A prospective study evaluating the nephrotoxicity of colistin found a 14% incidence of acute renal failure (42–44). The interested reader is referred to a contemporary article that summarizes the current understanding of colistin pharmacokinetics and pharmacodynamics (106).

Tetracyclines (both minocycline and doxycycline) have also been used as therapy for VAP caused by MDR *A. baumannii* (227). Tigecycline may find a useful role in this infection (113), as it achieves excellent penetration in tissues (including the lung but excluding the urinary tract). A recent report describes the successful treatment of septic shock due to pan-resistant *A. baumannii* using tigecycline to supplement a failing regimen of meropenem and colistin (194). However, the MIC required for *A. baumannii* (2 µg/ml) is higher than the achievable peak serum concentration, and this may limit its utility in bloodstream infections. Bloodstream infection caused by non-tigecycline-susceptible *A. baumannii* occurring in patients receiving tigecycline for other indications was recently reported in Pittsburgh (144). Trials are currently planned to evaluate the use of tigecycline for serious bloodstream infections and VAP.

How does one reconcile the in vitro, animal model, and clinical data? It is unfortunate that the studies cited do not allow one to draw firm conclusions. These disparate findings may reflect the lack of standardization in our approach to these problems or the vast genetic heterogeneity of *Acinetobacter* spp. The fundamental question regarding the virulence of this organism, whether it merely represents a marker of critical illness or if it indeed has a discrete attributable mortality, remains unanswered. Nevertheless, based upon careful clinical

consideration, it is our opinion that monotherapy with ampicillin/sulbactam or a carbapenem (imipenem or meropenem) is adequate for the treatment of infections caused by imipenem- or ampicillin-sulbactam-susceptible *Acinetobacter* spp. When carbapenem resistance is suspected, we recommend that intravenous colistin be combined with rifampin and imipenem. This recommendation is based upon studies summarized here that examine activity against carbapenem-resistant isolates lacking MBLs by use of Etest strips (230). Where the dissemination of MBLs accounts for the increasing prevalence of carbapenem-resistant *A. baumannii*, the combination of colistin and rifampin (with or without tigecycline) should be considered, along with the administration of nebulized colistin as part of a combination regimen in VAP. We also strongly urge that careful attention be given to accurate susceptibility testing (51, 82, 193).

On the horizon. Regrettably, there are few antibiotics for the treatment of infections caused by MDR *A. baumannii* on the horizon (195). Recent studies that examined the use of a specific antimicrobial peptide that is bactericidal against *A. baumannii* are provocative. Two cationic membrane-active antimicrobial peptides have been used to inhibit the growth of *A. baumannii*: rBPI₂ (Neuprex; XOMA Corporation, Berkeley, CA) and cecropin P1 (Sigma, St. Louis, MO). The former is a recombinant form of the N-terminal domain of the human bactericidal permeability-increasing protein, and cecropin is an antibacterial peptide (10, 11, 214). The application of these agents in the treatment of serious *Acinetobacter* infections in the clinic remains undefined, as peptides have major cost, manufacturing, delivery, and toxicity issues that will need to be overcome.

PERSPECTIVES ON CONTROL OF MDR *A. BAUMANNII*

Given the tremendous challenge posed by MDR *A. baumannii* and the predictable emergence and dissemination of mechanisms of resistance to any existing agent, solutions beyond the paradigm of antibiotics should be aggressively explored (29). Among these, infection control is crucial, particularly given the ability of *A. baumannii* to cause outbreaks. Contact precautions, handwashing, and alcohol hand decontamination, although universally encouraged, are seldom applied rigorously. Their importance, however, cannot be overstressed (14, 149). We favor the application of meticulous environmental decontamination and aggressive chlorhexidine baths as temporary measures to control outbreaks. We are cognizant that these measures are expensive, are labor-intensive, and must be proven in prospective trials. However, the virtue of infection control measures rests with preventing dissemination of MDR clones.

The application of molecular tools in the investigation of outbreaks to establish clonality among isolates permits a more effective deployment of infection control measures and aids in the identification of environmental sources (117, 224). The current accepted practice is to use either pulsed-field gel electrophoresis or repetitive extragenic palindromic sequence-based PCR. The recent addition of analysis of repetitive extragenic palindromic sequence-based PCR fragments by the Bacterial Barcodes System promises to perform as well as these labor-intensive methods (168). Most recently, PCR fol-

lowed by electrospray ionization mass spectrometry and base composition analysis has been applied to the determination of clonality (38, 74). PCR and electrospray ionization mass spectrometry can be done in less than 4 h. This technology may prove to be the premier method to determine bacterial identity and clonality.

Restriction of the use of antibiotics, especially those with broad-spectrum activity and those identified as antibiotics of last resort, is a necessary complement to any infection control strategy. The implementation of systems to monitor antimicrobial resistance and its relationship to antimicrobial use, as well as a program of antimicrobial stewardship, has been recommended. These are likely to have an impact on MDR *A. baumannii*, particularly as specific drugs favoring the emergence and dissemination of this organism are identified and restricted (140).

The refinement of genomic and proteomic techniques represents promise not only for the discovery of new antimicrobials active against MDR organisms but also for the development of vaccines (21, 72). Marti et al. have applied proteomic analysis to fractions enriched with *A. baumannii* cell envelopes (120). An intriguing report regarding the safety and immunogenicity of an oral, whole-cell *P. aeruginosa* vaccine was recently published (30). Here the investigators showed that important immunological markers of protection were achieved. Provocative studies used surface-expressed immunodominant bacterial polysaccharides of *P. aeruginosa* administered intranasally to confer immunity to mice (35). This raises interest in the potential application of this method to *A. baumannii*. Others have also shown that killed but metabolically active vaccines stimulate strong immune responses (16, 96). As interest in and knowledge about *A. baumannii* continue to increase, similar endeavors with that organism are conceivable. Short-term immunity would also be an attractive option, for instance, for military personnel deployed to Iraq or Afghanistan. Immunization may reduce the bacterial load and reduce the number of days a hospitalized patient is colonized. The success of these and other approaches for the containment of MDR *A. baumannii* depends on the commitment of clinical practitioners, scientists, and hospital and public health administrators and on the support of an informed and concerned public.

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