Considerations in Control and Treatment of Nosocomial Infections Due to Multidrug-Resistant *Acinetobacter baumannii*

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We sought to control infection due to multidrug-resistant *Acinetobacter baumannii* (MDR-Ab) by identifying isolates as clonally related, leading to enhanced infection-control measures, including cohorting, surveillance, contact precaution, initial therapy with ampicillin/sulbactam and local polymyxin B, and, more recently, therapy with synergistic antibiotic combinations. Class restriction of cephalosporins has been associated with a reduction in cephalosporins-cephamycin-carbapenem resistance among nosocomial *Klebsiella* isolates. This has been supplemented by restriction of carbapenem use after an initial 24-h period in an effort to reduce the selection of porin-deficient, carbapenem-resistant *A. baumannii* and *Pseudomonas aeruginosa*. Evidence is reviewed suggesting that eradication of MDR-Ab nosocomial colonization may prevent subsequent infection. Relatively few standard antibacterial drugs remain active against MDR-Ab. Published clinical results of therapy with these agents are reviewed, and in vitro evidence of synergy between them is presented that suggests that combination therapy should be studied for enhanced clinical activity.

Increasing isolation of multidrug-resistant *Acinetobacter baumannii* (MDR-Ab) has been reported worldwide, and it is now one of the most difficult nosocomially acquired gram-negative pathogens to control and treat [1–3]. Once detected within specific areas of the hospital, various levels of intervention have been attempted to reduce the incidence and prevalence of infection due to MDR-Ab. Physicians are also facing challenging therapeutic quandaries when treating patients infected with MDR-Ab, because the increasing prevalence of resistance continues to restrict their treatment options. Here, we describe the roles of infection control, antibiotic therapy, and decolonization strategies that have helped or might support the management of infections caused by MDR-Ab. In addition, various antibacterials that have demonstrated efficacy both in vitro and in

vivo will be presented to help guide practicing physicians expand their choices for treatment of MDR-Ab infection.

EPIDEMIOLOGY

The capacity of *Acinetobacter* species to survive on most environmental surfaces for long periods of time suggests that all animate and inanimate entities should be considered reservoirs. Although studies of hand carriage in *Acinetobacter* species show that it is a transient phenomenon in temperate climates, a report by Anstey et al. [4] demonstrated wet season throat carriage in 10% of Australian community residents. Several deaths were attributed to community-acquired bacteremic pneumonia in this setting, and PFGE analysis implicated many *Acinetobacter* strains. This is in contrast to the findings of most epidemiological surveys, which have demonstrated the predominance of one or a few hospital-specific endemic clones [1]. Interhospital transmission of several predominant clones of MDR-Ab has also been documented [5]. The constant verification of clonality involved in most nosocomial outbreaks directly links their spread to breaches in infection-control practices.

MECHANISMS OF RESISTANCE IN *ACINETOBACTER* SPECIES

To date, *A. baumannii* isolates containing plasmid-mediated class B metalloenzymes that hydrolyze all β-lactam antibiotics except aztreonam (IMP or VIM family) have been reported from diverse geographical areas, including Japan, Italy, Hong Kong, and Korea (table 1) [6]. Resistance of *A. baumannii* to carbapenems among isolates from the United States and Canada is, in contrast, caused primarily by a combination of chromosomally associated β-lactamases and porin protein mutations [1]. However, a recent report from Canada documented a variation of the IMP enzyme (IMP-7) in *Pseudomonas aeruginosa*, and VIM-4 has recently been identified in *P. aeruginosa* from Texas [9]. Clinical microbiology laboratories in the United States should be extremely vigilant for the imminent detection of plasmid mediated metalloenzymes in multidrug-resistant *A. baumannii* and other gram-negative species. An easy-to-perform detection procedure that uses Etest methodology (AB Biodisk) with one end of the strip containing imipenem and the other end possessing imipenem plus EDTA can be used to discriminate between metalloenzymes and other types of carbapenem resistance [10].

Class D OXA type enzymes, identified in both *P. aeruginosa* and *Acinetobacter* species, can also inactivate the carbapenems, but with less efficiency than the metallo–β-lactamases [6]. These enzymes are not inhibited by EDTA and may be difficult to detect in the standard clinical microbiology laboratory. The OXA-31 enzyme in *P. aeruginosa* preferentially hydrolyzes cefepime, but not ceftazidime [11]. Thus, such resistance may be missed if only ceftazidime were used to test susceptibility to late-generation cephalosporins. Therefore, both cefepime and ceftazidime should be used to detect all cephalosporin-resistant isolates.

MDR-AB AT NEW YORK HOSPITAL QUEENS

In 1988, we noted that many of our *Acinetobacter* isolates were resistant to all antibiotics except ceftazidime, imipenem, and aminoglycosides. Unrestricted use of ceftazidime for *Acinetobacter* infections then selected for ceftazidime-resistant

Table 1. Mechanisms of β-lactamase resistance in *Acinetobacter baumannii.*

β-Lactamase or other mechanism	β-Lactam(s) affected	Genetic location	Molecular class	Reference(s)
OXA-23	Penicillins, cephalosporins, carbapenems	Chromosome/plasmid	D	[6, 7]
OXA-24	Penicillins, cephalosporins, carbapenems	Chromosome (not USA[a])	D	[6, 7]
OXA-25	Penicillins, cephalosporins, carbapenems	Chromosome (not USA[a])	D	[6, 7]
OXA-26	Penicillins, cephalosporins, carbapenems	Chromosome (not USA[a])	D	[6, 7]
OXA-27	Penicillins, cephalosporins, carbapenems	Chromosome (not USA[a])	D	[6, 7]
OXA-40	Penicillins, cephalosporins, carbapenems	Chromosome (not USA[a])	D	[6, 7]
AMP-C	Penicillins, cephalosporins	Chromosome	C	[1]
CARB-5	Penicillins, cephalosporins	Chromosome	C	[1]
PER-1	Penicillins, cephalosporins	Plasmid	A	[1]
IMP-1	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
IMP-2	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
IMP-4	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
IMP-5	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
VIM-1	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
VIM-2	Penicillins, cephalosporins, carbapenems not aztreonam	Plasmid (not USA[a])	B	[6]
Altered PBP[a]	Imipenem	Chromosome		[1]
Absence of 29-kDa OMP[b]	Imipenem	Chromosome		[8]
Reduced expression of 33–36 kDa OMP[b]	Imipenem	Chromosome		[8]

[a] Enzyme has not yet been identified in isolates in the United States.
[b] Penicillin-binding protein.
[c] Outer membrane porin.

Klebsiella pneumoniae (CRKp) in 1989. Restriction of ceftazidime led to a 20% decrease in the prevalence of CRKp from 1989 to 1992 [12]. However, a clonal outbreak of ceftazidime- and imipenem-resistant *Acinetobacter* species developed, even though imipenem use was also restricted [13]. As this was occurring, the infection-control program responded by developing a more comprehensive approach to detecting multidrug-resistant organisms and monitoring interventional practices [12]. Currently, the antibiogram of all clinical gram-negative isolates is examined for resistance to ceftazidime and/or cefepime, and duplicates recovered from the same patient are excluded. Patient records are examined to determine whether the isolates represent colonization or infection and whether nosocomial acquisition has occurred. In contrast to *P. aeruginosa,* almost all nosocomial *Acinetobacter* strains exhibit ceftazidime resistance before they progress to carbapenem resistance. To date, acquisition of plasmid-mediated carbapenemases in *Acinetobacter* species has not been documented in the United States.

In 1991, we experienced a nosocomial outbreak of *Acinetobacter* infections that were susceptible only to the polymyxins and sulbactam. The outbreak occurred primarily in the surgical intensive care unit (SICU). Imipenem-resistant *A. baumannii* was isolated from various sources among 59 patients, 18 of whom were considered to be infected [13]. More than 50% of isolates were recovered from the respiratory tract. To identify possible sources of transmission, samples were obtained from the SICU environment and personnel for surveillance cultures. Although a variety of culture media and swabbing techniques have been reported previously, we used brain-heart infusion broth for environmental swabs and asked hospital personnel to rinse their hands in a specific reproducible manner in 100 mL of trypticase soy broth, which was contained in gallon-size plastic bags. After hand rinsing, the bags were sealed, incubated at 37°C for 24 h, and processed by standard microbiological methods.

Both environmental and personnel cultures from the SICU yielded strains of MDR-Ab that were either susceptible to imipenem alone or to imipenem and amikacin, or that were resistant to both imipenem and amikacin. All were resistant to other agents except polymyxin B and sulbactam, and all demonstrated similar restriction endonuclease patterns that indicated a clonal relationship. Samples obtained from laryngoscopes used in the SICU and the hands of respiratory therapists from the SICU yielded the same strains on culture. Samples obtained from other units in close proximity to the SICU had negative surveillance culture results. Intensive infection-control measures were then implemented, including a thorough cleaning of all objects and materials in the SICU, repainting the unit, instruction regarding proper hand washing techniques and glove changing to all members of the unit, cohorting of col-

onized and infected patients, and targeted infection-control education to all personnel who had positive hand culture results. Nurse cohorting was also implemented to as great a degree as possible. These actions, along with restriction of imipenem use, administration of ampicillin/sulbactam to selected patients, and use of polymyxin B for wound irrigation, eradicated imipenem-resistant *A. baumannii* from our hospital for >5 years (table 2). Several similar experiences from other health care centers have confirmed that such outbreaks usually occur in intensive care units, causing primary ventilator-associated pulmonary infection and bacteremia, and that they are clonal or oligoclonal in origin [1, 5]. Multifaceted approaches similar to those described above have been successful in most instances, thus limiting the need to close affected units.

During the past few years, we have identified both ceftazidime- and imipenem-resistant *A. baumannii* isolates from nursing home patients consistent with a recent finding that multidrug-resistant, gram-negative infections are frequently encountered in patients who reside in long-term care facilities [14]. Future studies are necessary to determine whether MDR-Ab colonization or infection within such facilities represents a source of dissemination to the acute care hospital setting. Although most hospitals

Table 2. Methods used to control nosocomial *Acinetobacter baumannii* infection at New York Hospital Queens.

Daily review of antibiotic susceptibility of all clinical isolates
    Select ceftazidime or cefepime- or carbapenem-resistant isolates (eliminate duplicates from the same patient)
    Review patient records prospectively to determine geographic location, nosocomial acquisition, and presence of clinical infection
Emphasize contact precautions to prevent transmission of isolates
    Assign a dedicated infection-control nurse to affected area or areas
    Cohort colonized and infected patients
    Make alcohol-based soaps readily accessible
    Enforce personnel hand washing by periodic culturing of hand samples
Use polymyxin B to selectively decontaminate colonized wounds
    Consider inhaled polymyxin B for pulmonary colonization or infection (to supplement parenteral therapy)
Use surveillance techniques to monitor personnel, equipment, and environmental contamination
    Instruct housekeeping to decontaminate the inanimate environment on a regular schedule
    Close contaminated unit if necessary
Use molecular epidemiologic techniques to determine clonality of isolates
Educate personnel on a continuous basis
    Provide surveillance results and infection rates in a timely manner to medical and surgical staff
    Provide ready access of infection-control staff to medical personnel, patients, and families for questions

have adopted standardized infection-control practices and policies during the past 2 decades, long-term care facilities lag behind because of fewer highly trained personnel and lack of on-site microbiology laboratories [15]. Thus, outbreaks of multidrug-resistant bacteria may occur without detection. Although outbreaks of multidrug-resistant *Acinetobacter* infection have not been reported from long-term care facilities, their future occurrence is likely in view of increasing resistance in this setting among gram-negative species [14]. Efforts to establish a national surveillance of health care–associated infections in the home-care setting have recently been addressed [16]. Individual hospitals and their associated extended care facilities should also record institution-related antibiotic susceptibility data to guide physicians and infection-control personnel in a focused manner. As one prominent investigator has stated, "national or global surveillance and strategy develop from local information and understanding" [17, p. 52].

EVOLUTION OF RESISTANCE AND CONTROL OF ANTIBIOTIC USE

After eradicating MDR-Ab from our institution in 1992, resistance to the cephamycins due to a novel AMP-C type, plas-

mid-mediated β-lactamases in many of our *K. pneumoniae* isolates was detected in 1994. Eight of these isolates further progressed to carbapenem resistance in combination with porin protein mutations. Escalating resistance among *Klebsiella* prompted us to class-restrict all cephalosporin and cephamycin use hospitalwide to remove the selective pressure for late-generation resistance in both *K. pneumoniae* and *A. baumannii* [12]. This resulted in a significant decrease in the incidence of plasmid-mediated, polyclonal CRKp colonization and infection [12]. However, chromosomally mediated, clonal ceftazidime and carbapenem resistance in MDR-Ab isolates recurred, requiring enhanced infection-control measures (figure 1).

ERADICATION OF COLONIZATION

Several studies have indicated that colonization with multidrug-resistant, gram-negative bacilli is a frequent precursor of true infection [18]. Specific sites of colonization may be amenable to eradication strategies. Hand colonization contributes significantly to *Acinetobacter* transmission and can be controlled by proper hand washing, glove use, and use of antiseptic- or alcohol-based soaps [18]. Compliance has always been an issue,
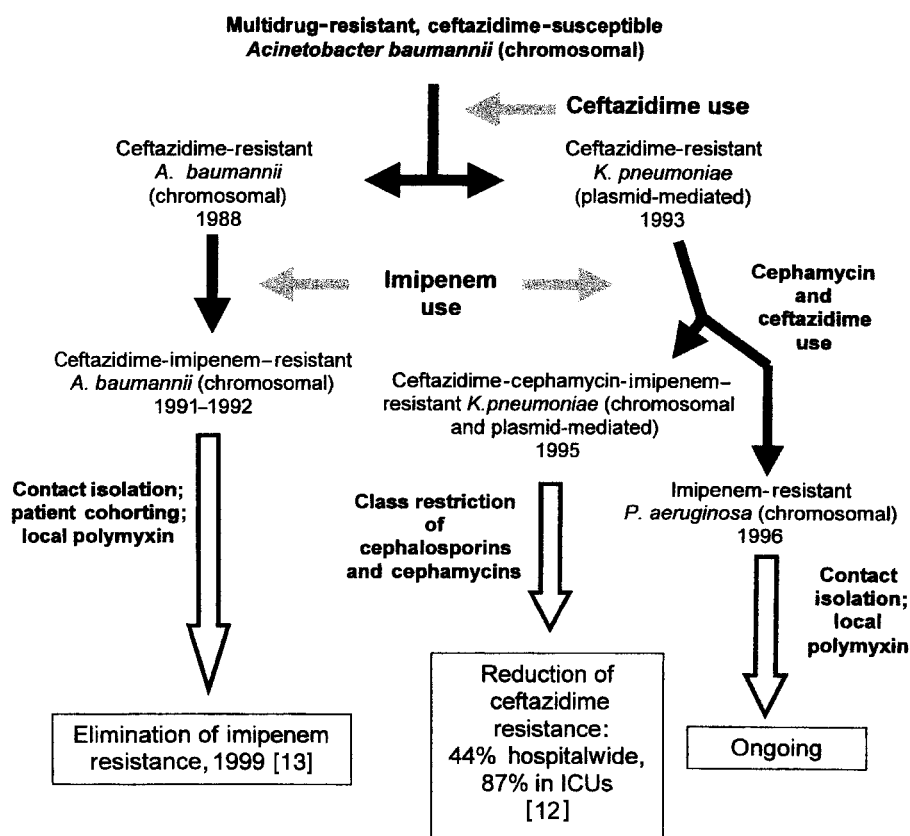

Figure 1. Evolution and control of antibiotic resistance among gram-negative bacilli at New York Hospital Queens. ICU, intensive care unit; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

and constant instruction and enforcement are necessary. At our institution, hand samples from health care workers are obtained for culture by our infection-control personnel without warning whenever an increasing frequency of problematic bacteria is recognized within specific hospital areas. Periodic use of this technique helps to reinforce the importance of hand washing and glove changing.

The digestive tract has only rarely been implicated as a major site for *Acinetobacter* colonization [19, 20]. If this is documented during an outbreak, selective decolonization with polymyxin B, other peptide antibacterials (investigational), or aminoglycosides could be attempted. Studies have shown that antibacterial prophylaxis with topical and systemic agents can decrease both respiratory tract infection and mortality in critically ill patients [21]. Aerosolized polymyxin and colistin have been used to prevent respiratory tract infections caused by *P. aeruginosa* in mechanically ventilated patients and patients with cystic fibrosis [22, 23]. This may be another option for reducing colonization and infection due to MDR-Ab. Careful monitoring of polymyxin inhalation is warranted, because acute respiratory insufficiency has occurred, and intrinsically resistant bacterial species *(Serratia* and *Proteus)* may emerge [22, 23]. A recent study of oropharyngeal rinsing with the investigational peptide antibacterial, iseganan, revealed reductions in microbial counts in oral secretions obtained from patients in an intensive care unit [24]. Further study of this technique is necessary to determine whether it will decrease the incidence of nosocomial pneumonia.

IN VITRO STUDIES OF ANTIBACTERIAL DRUGS

Although many *Acinetobacter* strains are susceptible to a wide variety of antibacterials, those causing nosocomial outbreaks of infection are usually susceptible only to ceftazidime, cefepime, sulbactam, imipenem, meropenem, amikacin, polymyxin B, and colistin (polymyxin E). However, increased use of cephalosporins and carbapenems has selected for hyperproduction of AMP-C type enzymes plus porin mutations in the United States and the OXA and metallo–β-lactamases in other areas of the world, thus reducing the efficacy of all β-lactam antibiotics [1, 6]. The activity of sulbactam against nosocomial *Acinetobacter* isolates is diminishing as well [5]. Polymyxin B and colistin remain the last resort among clinically available agents, with only rare reports of resistant isolates. However, in an earlier study, the MIC of colistin for clinical isolates of *Acinetobacter* was 1.0–128 μg/mL, indicating the presence of a few colistin-resistant isolates at that time [25]. Two recent studies have reported clinical isolates of *Acinetobacter* resistant to polymyxin B, one of which was recovered during the use of polymyxin B as monotherapy [5, 26].

A rapidly expanding group of natural and synthetic peptides from a variety of sources has shown in vitro activity when tested against multidrug-resistant nosocomial isolates of *A. baumannii* [27]. One such peptide, designated "bactericidal/permeability-increasing protein" (BPI), has exhibited killing activity against a wide range of gram-negative bacilli, as well as endotoxin binding properties [28]. We, in collaboration with others, showed that recombinant BPI_{21}, as well as cecropin P1, has in vitro activity against a clinical isolate of polymyxin B resistant *A. baumannii* [26]. A cecropin A–melittin hybrid has also demonstrated increased efficacy as compared with polymyxin B against a multidrug-resistant *Acinetobacter* strain [29].

Many in vitro studies have demonstrated synergy when polymyxin B is combined with imipenem, meropenem, azithromycin, rifampin, trimethoprim-sulfamethoxazole, rifampin, or ampicillin/sulbactam (table 3) [1]. Rifampin plus imipenem and rifampin plus ticarcillin-clavulanate-sulbactam have shown in vivo efficacy in mouse model experiments [31]. Earlier in vitro studies that used polymyxin B and rifampin against *Proteus* species and *Serratia marcescens* (both of which are intrinsically resistant to polymyxin B) also demonstrated synergy [32, 33]. These findings support the possibility that combination therapy for multidrug-resistant *Acinetobacter* infection may be more effective than monotherapy and may prevent selection of further resistance [34].

CLINICAL STUDIES OF ANTIBACTERIALS

Two recent retrospective studies compared ampicillin/sulbactam and imipenem-cilastatin for treatment of *Acinetobacter* ventilator-associated pneumonia [35] and bacteremia [36]. In the first study, clinical isolates were found to be resistant to imipenem-cilastatin, and ampicillin/sulbactam proved to be efficacious in a limited number of patients. The second investigation concluded that ampicillin/sulbactam was as effective as imipenem-cilastatin in patients with similar severity of illness. A third study compared sulbactam (3 g q.d.) and sulbactam/ampicillin (3 g/6 g provided in 3 divided doses q8h)

Table 3. Agents frequently active against nosocomially acquired *Acinetobacter baumannii.*

Agent	Reference
Single agents: imipenem, meropenem, sulbactam, ampicillin/sulbactam, amikacin, polymyxin B, colistin	[1]
Synergistic or additive combinations (in vitro)	
Polymyxin B plus azithromycin, rifampin, sulfamethoxazole-trimethoprim, imipenem, or meropenem	[5]
Sulbactam plus rifampin, azithromycin, or trovafloxacin	[30]
Rifampin plus imipenem or ticarcillin-clavulanate-sulbactam	[31]

[37]. No synergy was observed between ampicillin and sulbactam, and sulbactam alone was shown to be bacteriostatic when killing curves were performed. The authors suggested a role for sulbactam in non–life-threatening infections caused by *A. baumannii*. Therapy with ampicillin/sulbactam also yielded cure or improvement among 27 of 40 patients with severe nosocomial *Acinetobacter* infection, including cure of 6 of 8 patients with meningitis [38]. We have used ampicillin/sulbactam successfully against imipenem-resistant strains in selected patients. Sulbactam was shown to be bactericidal in vitro against these isolates [13]. Ampicillin/sulbactam remains a reasonable treatment modality for patients infected with susceptible *A. baumannii*. At least 6 g of sulbactam should be used as a daily dose for treatment of serious nosocomial infection due to this organism [36–38].

Polymyxin B and colistin have been used successfully in a limited number of patients infected with MDR-Ab, including those with ventriculitis, meningitis, pneumonia, and urinary tract– and catheter-associated disease [1]. A recent case report documented the successful treatment of a 14-year-old boy who was provided 1,000,000 IU of colistin iv q6h (5 mg/kg) to treat MDR-Ab meningitis [39]. The study showed that colistin penetrated the CSF at one-quarter the serum levels (1.25–5.0 μg/mL) without adverse effects. However, the use of these potent, last-resort antibacterials as single agents may cause the microorganisms to select for resistance.

Earlier investigations demonstrated success with 2- and 3-drug combinations for treatment of multidrug-resistant, gram-negative infections other than MDR-Ab. One study demonstrated cures in 8 of 12 patients infected with multidrug-resistant *Serratia marcescens* by giving polymyxin B (1.25 mg/kg iv q12h) with rifampin (20 mg/kg po). The MIC of polymyxin B alone for the 12 patients' isolates, as well as for an additional 40 clinical isolates, was $\geq$100 μg/mL. The MIC of rifampin was >6.25 μg/mL. Synergy was demonstrated in 51 of the strains that were inhibited by both agents at 3.1 μg/mL [32].

Trimethoprim-sulfamethoxazole-colistimethate (colistin) was administered to 6 patients infected with multidrug-resistant *Serratia marcescens*. When 1600 mg of sulfamethoxazole and 320 mg of trimethoprim was provided daily by mouth along with 100–300 mg of colistimethate, clinical improvement or microbiological cure was observed in 4 of 6 patients [40]. A combination of trimethoprim-sulfonamide and polymyxin B has also demonstrated bactericidal activity against 11 strains of *Pseudomonas cepacia*, even though the isolates were highly resistant to each agent [41].

Studies by Korvick et al. [42] have shown that the addition of rifampin to β-lactam agents and aminoglycosides for treatment of *P. aeruginosa* bacteremia had a positive trend in bacteriological response, compared with a β-lactam plus an aminoglycoside. They suggested that further studies should be performed. Although the number of patients in many of these studies was small, the reported results support future trials with 2 or 3 drugs in combination and the inclusion of rifampin for serious systemic infection caused by MDR-Ab.

In summary, MDR-Ab has established itself as one of the most difficult gram-negative pathogens to treat, because its most frequent victims are critically ill, are compromised by underlying surgical or metabolic disease, and are subject to invasive life-support measures, such as mechanical ventilation, intravascular catheters, renal dialysis, and surgical drainage systems. The clonal nature and spread of many outbreaks of MDR-Ab infection require close collaboration between infectious diseases, infection-control, intensive care, microbiology, pharmacy, housekeeping, and administrative personnel for effective control. Surveillance of antibiotic use and restriction of excessive late-generation cephalosporin use before development of resistance to these agents may prevent further evolution to carbapenem resistance. Innovative techniques to distinguish between pulmonary colonization and infection among ventilated patients would reduce the selection of resistant pathogens, such as *Acinetobacter* species, in the intensive care setting. Finally, the development of new, more potent antibacterial drugs directed against such pathogens has become increasingly problematic and should be relied on only as a last resort. These include a promising arsenal of peptide antibacterials with potent in vitro activity against MDR-Ab that should be studied further in clinical trials. The potential for improved activity of existing agents by combining those with synergistic in vitro effects should be investigated by controlled clinical studies.

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