Infections Due to Acinetobacter baumannii in the ICU: Treatment Options

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Semin Respir Crit Care Med 2017;38:311–325.

Abstract

Bacteria within the genus Acinetobacter (principally A. baumannii-calcoaceticus complex [ABC]) are gram-negative coccobacilli that may cause nosocomial infections in critically ill or debilitated patients (particularly ventilator-associated pneumonia and infections of the bloodstream, urinary tract, and wounds). Treatment of Acinetobacter infections is difficult, as Acinetobacter spp. are intrinsically resistant to multiple antimicrobial agents, and have a remarkable ability to acquire new resistance determinants via mechanisms that include plasmids, transposons, integrons, and resistance islands. Since the 1990s, global resistance to antimicrobials has escalated dramatically among ABC. Global spread of multidrug-resistant (MDR)-A. baumannii strains reflects dissemination of a few clones between hospitals, geographic regions, and continents; excessive use of antibiotics amplifies this spread. Many isolates are resistant to all antimicrobials except colistin (polymyxin E) and tigecycline, and some infections are untreatable with existing antimicrobial agents. Antimicrobial resistance poses a serious threat to treat or prevent infections due to ABC. Strategies to curtail environmental colonization with MDR-ABD will require aggressive infection control efforts and cohorting of infected patients. Thoughtful antibiotic strategies are essential to limit the spread of MDR-ABC. Optimal therapy will likely require combination antimicrobial therapy of existing antibiotics as well as development of novel antibiotic classes.

Keywords

► multidrug resistance
► antimicrobial resistance
► Acinetobacter spp.
► Acinetobacter baumannii
► plasmids
► clonal spread
► carbapenemases

Microbiology

Bacteria within the genus Acinetobacter are encapsulated, non–lactose fermenting, oxidase-negative gram-negative coccobacilli that may cause infections in health care or community settings, particularly in patients with comorbidities or skin/soft-tissue injuries.1–3 More than 20 Acinetobacter species have been identified,1 but the vast majority of clinical infections are caused by organisms within the A. calcoaceticus-A. baumannii complex (ABC).1,4–6 This complex comprises four species; A. baumannii, A. nosocomialis, and A. pittii cause clinical infections in humans, whereas A. calcoaceticus is an environmental organism of negligible clinical significance.1 A. baumannii is the most common species in most regions; the prevalence of A. pittii and A. nosocomialis is higher in Southeast Asia and A. pittii may be more common in Scandinavian countries.6–8 A. baumannii has been associated with heightened mortality and a higher degree of antimicrobial resistance compared with other Acinetobacter spp.1,6,9

Clinical Features

Acinetobacter species (spp.) most frequently cause nosocomial infections in critically ill or debilitated patients,10,11 including ventilator-associated pneumonia (VAP),10,12–14 bloodstream infections (BSI),6,11,15 device-associated
infections (DAI),16 wound or skin and soft-tissue infections (SSTI),1,17 burns,18,19 urinary tract infections (UTI),1 intra-abdominal infections (IAI),17 and meningitis.1 Additionally, Acinetobacter spp. have been implicated in SSTI sustained during disasters, including earthquakes,20 tsunamis,21 terrorist attacks,22 and combat injuries in Vietnam,23 Iraq and Afghanistan,24,25 Ukraine,26 Lebanon, and Syria.1,27 Infections due to Acinetobacter spp. occur more frequently in subtropical or tropical regions; in temperate climates, infections are more common in the summer.1,24,28 Community-acquired pneumonia (CAP) due to ABC rarely occurs in temperate climates, but fulminant CAP, sometimes with septic shock, has been described in Asian-Pacific regions.3,29,31 Factors predisposing to ABC-associated CAP include alcoholism,32,33 diabetes mellitus, male gender, renal or pulmonary disease, cirrhosis, advanced age, smoking.3,31

**Prognosis of Infections Due to A. Baumannii**

Mortality rates with VAP or BSI due to Acinetobacter spp. are 30 to 75%; these high mortality rates in part reflect comorbidities and severity of illness.1,15,34–37 In the EPIC II study, a multinational study of 14,414 ICU patients, infection with ABC was independently associated with a greater risk for hospital death (odds ratio [OR]: 1.53, p < 0.001).38 Within the past three decades, resistance rates among ABC have escalated globally.1 Emergence of multidrug-resistant (MDR) strains has undoubtedly contributed to mortality. Not surprisingly, inappropriate initial empiric antibiotic therapy (IET) for pneumonia or sepsis due to ABC has been associated with heightened mortality.39–41 In a recent retrospective review of 1,423 patients hospitalized with sepsis or pneumonia due to ABC, 82.3% of isolates were MDR.40 MDR-ABC strains have been implicated in Asian-Pacific regions.4,32,33 Factors predisposing to ABC-associated CAP include alcoholism, diabetes mellitus, male gender, renal or pulmonary disease, cirrhosis, advanced age, smoking.3,31

**Infections Due to ABC in the Hospital Setting**

**ICU Infections**

Most ABC infections occur in hospitalized patients in the ICU, often with multiple comorbidities. Device-related infections (DRI) are typical (i.e., VAP, central venous catheter [CVC]-associated BSI, surgical site infections [SSI], catheter-associated UTIs). The EPIC II point prevalence study in 2007 comprising 75 countries implicated Acinetobacter spp. in 8.8% of all ICU infections, with rates of 19% in Asia and 17% in Eastern Europe.38 In the SENTRY study from January 2009 to December 2011, ABCs were implicated in 7% of ICU infections in the United States and Europe.44 Even higher rates of ABC infections have been reported in Latin America45,46 and Asia.17,47,48 In a review of Vietnamese pediatric ICUs, ABC was implicated in 18.4% of hospital-acquired infections (HAI); 65% of isolates were carbapenem resistant (CPR).49 In a prospective study from six hospitals in Iran (2011–2012), ABC was implicated in 35% of DRI among hospitalized adults.16 Importantly, 70.5% were CPR.

**Hospital-Acquired Pneumonia**

ABC is a common cause of ICU-acquired pneumonia, accounting for 8 to 14% of VAP in the United States50 and Europe,51 but much higher rates (19% to >50%) in Asia,52 Latin America,53 and some Middle Eastern54 countries. In the United States, rates of VAP due to ABC increased from 4% in 1986 to 7.0% in 2003; no increase was observed for any other gram-negative bacilli.55 Data from 463 hospitals in the United States from January 2006 to October 2007 implicated A. baumannii in 8.4% of VAP.50 In a study of 411 cases of VAP from nine European countries, A. baumannii was implicated in 13.9% of cases.51 In a cohort of 827 cases of VAP in 27 ICUs in Europe, A. baumannii was implicated in 11% of early-onset and 26.5% of late-onset VAP.56 In Greece and Turkey, ABC was the most common cause of VAP.56 One prospective study in Turkey implicated ABC in 54% of VAP.54 Rates of VAP due to ABC are high in tropical or subtropical regions, particularly in Asia. In a series of 621 cases of VAP in Japan from 2005 to 2011, Acinetobacter accounted for 54.3% of cases.52 A prospective study in 10 Asian countries from 2008 to 2009 of VAP in adults (n = 2,554) implicated Acinetobacter spp. in 36.5% of cases.47 Importantly, 67.3% of Acinetobacter spp. isolates were resistant to imipenem.47

**Risk Factors for Colonization or Infection with Acinetobacter spp.**

In critically ill patients, Acinetobacter spp. may colonize the gastrointestinal (GI) tract, skin, and respiratory tract, and may cause serious infections.1,24 Risk factors for acquisition of Acinetobacter spp. include invasive procedures or devices, prolonged ICU stay, mechanical ventilation (MV), enteral feedings, burns, and recent use of broad-spectrum antibiotics, particularly cephalosporins (CEPHS) or fluoroquinolones (FQs)1,24,34,57,58 (Table 1). A prospective study identified the following independent risk factors for ICU-acquired A. baumannii: (1) prior occupant in that room with A. baumannii (OR: 4.2, p < 0.001) and (2) MV (OR: 9.3, p < 0.05).59 Diabetes mellitus may increase the risk of recurrent or persistent colonization with ABC.60 Risk factors for ABC bacteremia among ICU patients include colonization with ABC; high APACHE II scores; MV; presence of an endotracheal tube; recent invasive procedures; CVCs; and prior antimicrobials.1 In one study, colonization of CVCs with MDR-ABC was associated with a 28% risk of subsequent bacteremia.61 Studies in patients with malignancies cited the following risk factors for A. baumannii infection: CVC and nasogastric tubes,62 admission to the ICU63 dialysis, and prolonged ICU stay64; hematology malignancies; use of cefepime; and use of total parenteral nutrition (TPN).57 In neonatal ICUs, low birth weight, TPN, and presence of CVCs were risk factors for bacteremias due to ABC compared with uninfected infants.65
Mechanisms of Antimicrobial Resistance

*Acinetobacter* spp. have innate (chromosomal) resistance mechanisms against multiple antimicrobials but also can acquire new resistance determinants via mobile genetic elements such as plasmids, transposons, integrons, insertion sequences, and resistance islands.\(^1\)–\(^3\,\)\(^69\)–\(^72\)–\(^74\) Mechanisms of antimicrobial resistance are numerous and include (1) enzymatic inactivation or modification of antimicrobials; (2) alteration in the bacterial target site(s); (3) permeability barriers to uptake of antimicrobials; (4) active efflux pumps (that extrude antibiotics from bacterial cells); (5) combinations of mechanisms, which may occur as the result of large genomic islands containing multiple resistance genes.\(^1\)–\(^3\,\)\(^70\)\(^72\)

Global Escalation of Antimicrobial Resistance

Within the past three decades, antimicrobial resistance rates among ABC have escalated dramatically worldwide.\(^1\)\(^72\)–\(^75\) In some countries, more than 90% of ABCs are MDR.\(^1\)\(^7\) Molecular-based strain typing by pulse field gel electrophoresis (PFGE) or multilocus sequence typing (MLST) methods has documented global spread of MDR "epidemic clones" between hospitals, regions, and continents.\(^72\) International spread has been extensively documented: for example, between Brazil and Argentina;\(^76\) from Iraq to Germany and the United States among military personnel;\(^77\),\(^78\); from northwestern Europe to the Czech Republic and globally;\(^79\); from Turkey to Europe, the Middle East, and the rest of Asia;\(^80\); from southern to northern Europe, the Middle East, rest of Asia, and Latin America;\(^81\); from Europe to multiple continents.\(^34\) The rate of increase may be amplified by selection pressure from antimicrobial use, crowding, lack of hygiene, and increased worldwide travel.\(^24\),\(^34\)

Impact of Antimicrobial Use on Antimicrobial Resistance

Not surprisingly, the use of broad-spectrum antimicrobials has been linked to emergence of antimicrobial resistance. In the early 1990s, the use of imipenem against cephalosporin-resistant *Klebsiella pneumoniae* was associated with emergence of imipenem-resistant ABC in one New York hospital.\(^82\) Further, in multiple hospitals in Brooklyn, New York, there was an association between the use of third-generation CEPHS and aztreonam and CP-resistant ABC.\(^83\) In one case–control study in a surgical ICU, risk factors for acquisition of imipenem-resistant (IR) and imipenem-susceptible (IS) strains of *A. baumannii* were assessed.\(^84\) Risk factors for IR-ABC were ICU stay (OR: 8.1), prior exposure to imipenem (OR: 9.2), and prior exposure to third-generation CEPHS (OR: 2.1). Risk factors for IS-ABC include ICU stay (OR: 8.1) and prior exposure to third-generation CEPHS (OR: 2.1). Regionally and globally, selection pressure is the key determinant of emergence of CPR or MDR-ABC.

### ABC Virulence Factors and Pathogenesis

The virulence mechanisms and pathogenesis of *A. baumannii* infections have been reviewed elsewhere.\(^69\),\(^70\) *A. baumannii* has simple growth requirements and may survive in dry and desiccated conditions for prolonged periods.\(^1\)\(^69\)–\(^69\) Further, *A. baumannii* is able to adhere to living or inert surfaces and form biofilms.\(^1\)\(^2\) Additional bacterial factors that may heighten survival and virulence include outer membrane porins, capsule, lipopolysaccharide, regulatory proteins, and iron acquisition systems.\(^1\)\(^2\)\(^71\)

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Resistance to β-Lactams

β-Lactamases

All A. baumannii strains possess a chromosomal AmpC cephalosporinase that confers resistance to penicillins and early-generation cephalosporins (CPEPHS); however, under normal circumstances, resistance to third- and fourth-generation CEPHS due to AmpC is clinically insignificant. Clinically significant resistance may develop via hyperproduction of the AmpC cephalosporinase, the presence of insertion sequences that promote β-lactamase activity, or incorporation of mobile resistance genes.

β-Lactamases are categorized based on molecular structure into groups A through D and functionally into three groups (1–3) based on the target enzyme they degrade. Group 1 (class C) cephalosporinases are relatively narrow spectrum. Group 2 (classes A and D) include serine β-lactamases and extended-spectrum β-lactamases (ESBLs) and have a broader spectrum of activity. Group 3 enzymes include metallo β-lactamases (class B), which are potent hydrolyzers of CP and are not inhibited by β-lactamase inhibitors. β-Lactamases of the IMP, VIM, SIM, and NDM-1 families fall within Group 3.

Extended-Spectrum β-Lactamases

Numerous extended-spectrum β-lactamases (ESBLs) including SHV, TEM, PER, VEB, GES, and CTX-M confer high-grade resistance to all CEPHS. ESBL clones (TEM or SHV) were initially described in Enterobacteriaceae in France and Belgium in the late 1980s and mid-1990s, and rapidly spread globally. By the late 1990s, other plasmid-encoded ESBLs (e.g., PER-1, VEB, CTX-M, and GES) were described among Enterobacteriaceae and Acinetobacter spp. ESBL-containing plasmids (PER-1 type) among A. baumannii (as well as P. aeruginosa, and Klebsiella spp.) were first recognized in the late 1990s in Turkey and France, and spread globally. Clusters of ABC infections due to VEB-1 type ESBL were noted among French hospitals in 2003. Rapid clonal spread to Belgium, Argentina, Lebanon, and globally ensued. Other ESBLs identified in ABC include TEM-92 and -116 from Italy and the Netherlands, respectively; SHV-12 from China and the Netherlands, CTX-M-2 and CTX-M-43 from Japan and Bolivia, respectively. Later, CTX-M ESBLs were detected in India, Haiti, Brazil, and globally.

Carbapenemases

Many β-lactamases (including ESBLs) may also have hydrolytic activity against CPs via production of carbapenemases (CPE). The emergence of carbapenemases has created a major “hole” in antibiotic coverage against ABC. Carbapenemases include group 2 class D oxacillinases (e.g., OXA enzymes) and class B metallo-β-lactamases (MBLs) (e.g., IMP, VIM, and SIM-1 groups) and the newer CPE (i.e., KPC-like; GES-like, New Delhi metallo-β-lactamase-1 [NDM-1]).

Class D Serine Carbapenemases

Globally, the most common CPE in A. baumannii are the class D serine oxacillinases (OXA), represented by the OXA-23-, OXA-58-, and OXA-143-like types that can be encoded on chromosomes or plasmids. The first CPE (an OXA-type enzyme) in ABC was discovered in Scotland in 1985. By the mid-1990s, CPR-ABC clones (principally OXA-type CPE) were noted in Latin America, the United Kingdom, Europe, Australia, Africa, the Middle East, and Asia. In 2003, the OXA-58 oxacillinase (blaOXA-58 gene) was isolated from a CPR-Acinetobacter strain in Toulouse, France. Subsequently, OXA-58–producing CPR-ABC strains were reported in other Mediterranean countries (e.g., Lebanon, Turkey, and China). After 2009, ABC-producing OXA-23 (blaOXA-23 gene) became the dominant OXA in Europe, United States, Latin America, and globally. Three clonal lineages (known as Worldwide Clones 1, 2, and 3) dominate among clinical isolates of MDR-ABC globally.

KPC, a CPE, first reported in 1996 in K. pneumoniae in North Carolina, spreads rapidly within the northeastern United States and to France, Israel, Greece, Italy, and globally. KPC is encoded on plasmids in Enterobacteriaceae and P. aeruginosa, but has not widely disseminated among ABC. KPC-producing ABCs were detected in 10 isolates of A. baumannii in Puerto Rico in 2010. To our knowledge, KPC-producing ABCs have not been reported in other countries.

A newer group of CPEs termed GES (Guiana extended-spectrum β-lactamases) was first identified in K. pneumoniae in 2000, and later reported in Acinetobacter spp. in France in 2009, followed by rapid spread to Belgium, the Middle East, and Northern Africa. A novel CPE, termed NDM-1, was first detected in a K. pneumoniae isolate in a Swedish patient transferred from India. Retrospective studies showed that NDM-1 had been endemic among K. pneumoniae and Escherichia coli in Indian hospitals since 2006. By 2010, NDM-1–producing Enterobacteriaceae had been found on five continents and linked to travel in India or Pakistan. In the United States, three cases of infections due to NDM-1–producing Enterobacteriaceae were reported in 2010; all three had recently received medical care in India. From 2010 on, numerous publications cited NDM-1–producing ABC in Europe, the Middle East, Africa, Asia, and the Americas. Epidemiological reviews suggest that the majority of infections due to NDM-1–producing ABC occur in India, Asia, the Middle East, and the Balkans. Berrazeg et al reviewed all publications of infections due to NDM-1–producing bacteria from 2009 to December 31, 2012, and identified 950 cases. Only 36 cases (3.8%) were due to ABC. Although infections due to NDM-1–producing ABC have been cited in Brazil, Paraguay, Argentina, and Honduras, NDM-1–producing ABC appears to be rare in the Americas.

Epidemiology and History of Antimicrobial Resistance among Acinetobacter spp.

In the 1970s, Acinetobacter spp. were usually susceptible to ampicillin, cephalosporins, carbapenems (CPs), and several antibiotic classes. By the 1980s, resistance to various classes of antibiotics appeared, but nearly all isolates remained
susceptible to CPs. In the early 1990s, carbapenem-resistant (CPR) strains emerged.\(^1\) Importantly, CPR-ABCs are often resistant to all classes of antimicrobials except colistin and tigecycline.\(^{1,34}\) Ominously, strains of *Acinetobacter* resistant to colistin and tigecycline have been reported.\(^{154,155}\) Drug resistance has an adverse impact on clinical outcomes. Compared with patients with CP-susceptible strains, patients with CPR-ABC infections have increased mortality and increased hospital and ICU length of stay.\(^1\)

In the United States (and globally), CPR-ABCs have escalated dramatically over the past two decades. In the National Nosocomial Infections Surveillance (NNIS) System, CPR-ABC (ICU isolates) in the United States increased from 0% in 1986 to 20% in 2002.\(^{53}\) In a survey of more than 300 hospitals in the United States, CPR-*A. baumannii* increased from 9% in 1995 to 40% in 2004.\(^{24}\) The MYSTIC Study surveyed changes in antimicrobial resistance from clinical isolates at 15 US hospitals over a decade; resistance to imipenem increased from 10% in 1999 to 48% in 2008.\(^{156}\) The Surveillance Network (TSN) database examined more than 55,000 isolates of *Acinetobacter* spp. in the United States from 2002 to 2008; CPR increased from 20.6% in 2002 to 49.2% in 2008.\(^{157}\) A survey of nine regions in the United States from 2005 to 2011 found that 30% of 2,900 isolates of ABC were MDR.\(^{158}\) Another study in the United States in 2010 noted that 50% of 514 clinical isolates of ABC were CPR.\(^{159}\) In the SENTRY study from 2009 to 2011, susceptibility rates to imipenem in the United States were 43% (ICU) and 63% (non-ICU) and in Europe 45% (ICU) and 56% (non-ICU).\(^{44}\)

Worldwide, rates of CPR-ABC have been highest in Greece, Taiwan, and Latin America,\(^{46,106,160–162}\) but remarkable differences between countries have been noted.\(^{17,163}\) A survey of 48 European hospitals (MYSTIC) in 2006 cited CPR in 42.5% of ABC clinical isolates.\(^{164}\) In the COMPACT study from 2008 to 2009 in Europe, the Middle East, and Africa, 49% of ABC isolates were resistant to imipenem.\(^{165}\) Resistance rates were higher in Turkey, Greece, Italy, Spain, and England (45–85%) compared with France, Germany, and Sweden (4–20%).\(^{163}\) In one tertiary care hospital in the United Kingdom, CPR among ABC bloodstream isolates (BSI) rose from 0% in 1998 to 55% in 2006.\(^{111}\) A survey of 11 countries in Latin America in 2011 found that more than 50% of ABC clinical isolates were CPR.\(^{160}\) In the SENTRY study of ABC isolates from 2006 to 2009, *global* CPR rates rose from 34.6% in 2006 to 59.8% in 2009.\(^{165}\) The SMART surveillance study of urinary tract and IAI ABC isolates from 48 countries from 2011 to 2014 cited MDR ranging from 47% in North America to more than 93% in Europe and the Middle East.\(^{17}\) In China, 58% of blood stream isolates of ABC in 2013 were CPR.\(^{112}\) The SMART surveillance study, comprising 48 countries from 2001 to 2014, evaluated CPR resistance among ABC isolates from intra-abdominal and UTI.\(^{17}\) The incidence of MDR-ABC was lowest in North America (47%) and ranged from 77 to 87% in Africa, Asia, and Latin America, and exceeded 93% in Europe and the Middle East.\(^{17}\) This extraordinary rate of CPR-ABC reflects selection pressure from antibiotic usage. The use of CPs has been associated with increased incidence of CPR-ABC.\(^{162,166}\) In one study, the prevalence of infections due to MDR-ABC fell 2.24-fold after implementing a policy of restricting CP use in the ICU.\(^{167}\)

### Treatment of Infections Due to *Acinetobacter* spp.

Nosocomial infections due to ABC have been associated with high mortality rates (particularly with BSI or VAP).\(^{24,34,35}\) Early appropriate antimicrobial therapy is critical.\(^{3,11,35}\) Optimal therapy for serious ABC infections has not been established,\(^{1}\) as prospective randomized trials have not been done. For BSI, removal of invasive devices within 48 hours may reduce mortality.\(^{11}\) For SSTI or SSIs, debridement is an essential part of therapy.\(^{24}\) Carbapenem, alone or combined with a second agent, has been considered the best therapy for ABC infections.\(^{1,34}\) However, the emergence of CPR strains limits the use of these agents as monotherapy for *empirical treatment when CPR is a consideration*. We believe a combination of a carbapenem plus colistin is appropriate as initial empirical therapy for serious *A. baumannii* infections when CPR is suspected.\(^{43}\) Other agents (e.g., β-lactam/β-lactamase inhibitors, cefazidime, or FQs) may be used, provided isolates are susceptible.

### Advanced Generation Cephalosporins

Third- and fourth-generation cephalosporins (e.g., cefazidime, cefepime) are not reliable for empirical treatment of infections due to ABC. Globally, only 20 to 40% of ABCs are susceptible to expanded spectrum CEPHS.\(^{17}\) CEPHS should not be used as empirical treatment for ABC infections, but may be considered for susceptible strains.

### Sulbactam

Among β-lactamase inhibitors, sulbactam has the greatest bactericidal activity against ABC.\(^{1}\) Ampicillin-sulbactam (A/S) (due to the sulbactam component) may be effective therapy for some strains of ABC.\(^{168}\) High-dose A/S and extended time of infusion may enhance bactericidal activity.\(^{169}\) Clinical data supporting the use of sulbactam are limited to small series.\(^{168,170}\) Sulbactam may display synergy against ABC when combined with other antibiotics (e.g., CP, colistin).\(^{171}\)

### Fluoroquinolones

Fluoroquinolones may be active against some strains of ABC, but globally, fewer than 30% of ABCs are susceptible to FQs.\(^{17}\) FQ resistance can emerge via mutations in the quinolone resistance determining regions (QRDR) of gyrA and parC genes and/or by overexpression of efflux pumps.\(^{59}\)

### Aminoglycosides

Aminoglycoside resistance among ABCs may emerge via the production of aminoglycoside-modifying enzymes, 16S ribosomal RNA methyltransferase (ArmA), or efflux pumps.\(^{1}\) In one French study, increased use of amikacin was associated with emergence of amikacin-resistant ABC; decreased amikacin use led to a decrease in case incidence.\(^{172}\) The
activity of aminoglycosides against ABC is variable, but resistance rates exceed 60% in most countries.\(^\text{173}\) See Table 2 for summary of antimicrobial resistance mechanisms among \textit{Acinetobacter} spp.

### Treatment of Infections Due to \textit{Acinetobacter} spp.

In view of the high incidence of MDR-ABC, initial empirical therapy with combination therapy (typically CP plus colistin) is often employed while awaiting antimicrobial susceptibility results. Optimal therapy is not clear, as randomized, controlled studies are lacking. In the next sections, we will discuss antibiotics that are often used either as monotherapy or part of combination therapy for MDR-ABC.

### Polymyxins (Colistin)

Polymyxins (e.g., polymyxin B and polymyxin E [colistin]) are cationic lipopeptides that disrupt the outer membrane of gram-negative bacteria and are rapidly bactericidal.\(^\text{155}\) Polymyxins are usually highly active against MDR-ABC, including isolates resistant to tigecycline.\(^\text{1}\) Colistin is administered intravenously as an inactive prodrug (colistimethate sodium [CMS]), whereas polymyxin B is an active drug. CMS is widely available, whereas polymyxin B is infrequently used. Resistance rates to colistin are generally low (<1%),\(^\text{174}\) but colistin resistance among ABCs has been increasing.\(^\text{155,175}\) In a survey of 514 ABC isolates from 66 sites in the United States and Puerto Rico in 2010, 5% of isolates were resistant to colistin.\(^\text{159}\)

Colistin can be administered by intravenous (IV) or inhaled routes.\(^\text{1}\) IV colistin has potential renal toxicity\(^\text{1}\) and neurotoxicity (principally paresthesias).\(^\text{1}\) Risk factors for nephrotoxicity include colistin dose > 5 mg/kg/day ideal body weight\(^\text{176}\) and concomitant use of rifampin or nephrotoxins.\(^\text{176}\) Optimal dosing regimens for IV colistin have not been established.\(^\text{1,177}\) Colistin exhibits a concentration-dependent bactericidal activity: therapeutic effect depends on the ratio of peak serum concentration to minimum inhibitory concentration (MIC) or the ratio of the area under the curve (AUC) to MIC.\(^\text{1}\) Strategies involving higher doses, longer dosing intervals, loading doses, extended infusions, and pharmacokinetic/pharmacodynamic (PK/PD) principles have been proposed to optimize efficacy and prevent the development of resistance.\(^\text{178–180}\) However, colistin has relatively poor PK/PD properties, and it may be difficult to achieve high enough serum concentrations quickly.\(^\text{155}\) CMS (a prodrug) has to be converted to the active form (colistin) in the plasma, and concentrations may be suboptimal for 2 to 3 days until a steady state is achieved; thus, a loading dose is recommended.\(^\text{1}\) One in vitro study suggested that achievement of serum levels more than 1 mg/L within 1 hour had significant bactericidal activity.\(^\text{181}\)

Studies reporting efficacy of colistin \textit{monotherapy} for ABC infections are limited. In a prospective study of 35 episodes of VAP due to MDR-ABC, patients were treated with imipenem \((n=14)\) versus colistin \((n=21)\) based on susceptibility testing.\(^\text{182}\) Cure rates were 57% in both groups; in-hospital mortality rates were similar (64 and 62%, respectively). The

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<th>Resistance mechanism</th>
<th>Target antimicrobial</th>
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<td>Aminoglycoside-modifying enzymes (AAC, APH, AAD)</td>
<td>Aminoglycosides</td>
<td>1,70</td>
</tr>
<tr>
<td>Modification of drug target site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{gyrA} and \textit{parC} mutations</td>
<td>Fluoroquinolones</td>
<td>1,69,70</td>
</tr>
<tr>
<td>Alteration of ribosomal-binding site (RmtB, ArmA)</td>
<td>Aminoglycosides</td>
<td>1,70</td>
</tr>
<tr>
<td>Altered lipid A of bacterial lipopolysaccharide (PmrAB two-component system mutation)</td>
<td>Colistin</td>
<td>1,70</td>
</tr>
<tr>
<td>Loss of lipopolysaccharide (mutated \text{lpa}A, \text{lpx}C, \text{lpx} D)</td>
<td>Colistin</td>
<td>1,70</td>
</tr>
<tr>
<td>Altered cell permeability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porin/outer membrane protein loss</td>
<td>Carbapenems, aminoglycosides</td>
<td>70</td>
</tr>
<tr>
<td>Efflux pumps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RND efflux pump (AdeABC, AdeFGH, Ade IJK, AbeM)</td>
<td>Fluoroquinolones, β-lactams, aminoglycosides, tetracyclines</td>
<td>1,70</td>
</tr>
</tbody>
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infections due to Acinetobacter baumannii in the ICU

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impact of combination therapy has not been elucidated. Turkish investigators retrospectively assessed clinical outcomes in 250 patients with BSI due to extremely resistant ABC.\textsuperscript{183} Thirty-six patients received colistin monotherapy; 214 received colistin plus a second agent. All isolates were susceptible to colistin. In-hospital mortality was lower in the combination group compared with monotherapy group (52.3% vs. 72.2%, \( p = 0.03 \)) and rate of microbiological eradication was higher in the combination therapy compared with monotherapy (79.9% vs. 55.6%, \( p = 0.001 \)). By multivariate analysis, Pitt bacteremia score, age, and duration of ICU stay were independent predictors of 14-day mortality. An observational study of 28 Spanish hospitals assessed 30-day mortality rates among 101 patients with serious infections due to MDR-ABC.\textsuperscript{184} Pneumonia was present in 50.5%. Sixty-eight patients received monotherapy (MT) (usually a CP or colistin); 33 received combination therapy (CT). Thirty-day mortality rates were similar (23.5% for MT; 24.2% for CT; \( p = 0.94 \)). Another observational study reviewed 69 organ transplant recipients either colonized (\( n = 28 \)) or infected (\( n = 41 \)) with XDR \textit{A. baumannii}.\textsuperscript{185} Among 41 patients with infections, 37 received antimicrobial therapy. Clinical success at 28 days was achieved in 18/37 (49%), but clinical recurrence developed within 3 months in 8 of 18 (44%) within 3 months. Further, colistin resistance developed in 5 of 14 patients. The use of combination therapy with colistin and a carbapenem was an independent predictor of survival.\textsuperscript{185} These various retrospective studies are inadequate to assess the role or benefit (if any) of combination therapy or the optimal agents to use for serious infections due to ABC.

Aerosolized (inhaled) colistin has been used in patients with cystic fibrosis and as adjunctive therapy for nosocomial pneumonia due to ABC, but data are limited to nonrandomized, retrospective studies.\textsuperscript{1,186} One randomized open-label trial compared the efficacy of nebulized CMS (plus IV colistin) for 100 patients with gram-negative VAP, 60% of which were due to ABC. Microbiological outcome was better with nebulized plus IV therapy (60.9%) compared with 38.2% among IV CMS only group (\( p = 0.03 \)). Importantly, clinical outcomes were similar (51.0 vs. 53.1%, \( p = 0.94 \)). Further, there were more episodes of bronchospasm in the nebulized plus IV therapy group (7.8 vs. 2.0%, respectively, \( p = 0.36 \)). The clinical benefit of nebulized CMS to treat VAP has not been established.

Resistance to colistin may develop.\textsuperscript{185} Plasmid-mediated resistance via \textit{mcr}-1 gene among \textit{Enterobacteriaceae} was first reported China,\textsuperscript{187} and human cases of \textit{E. coli} or \textit{Enterobacteriaceae} expressing \textit{mcr}-1 were described shortly thereafter in Switzerland,\textsuperscript{188,189} Canada,\textsuperscript{190} and Singapore.\textsuperscript{191} The \textit{mcr}-1 gene has not yet been identified in \textit{Acinetobacter} spp., but it is feasible that in time, MDR \textit{Acinetobacter} could acquire this resistance mechanism. Colistin heteroresistance may also occur.\textsuperscript{155} Colistin-resistant ABCs appear to have reduced fitness and less virulence,\textsuperscript{192} including a decreased ability to form biofilms.\textsuperscript{193}

\textbf{Tigecycline}

Tigecycline, a semisynthetic derivative of minocycline, has excellent in vitro activity against MDR-ABC (including CPR strains).\textsuperscript{194,195} However, clinical studies assessing efficacy of tigecycline for serious ABC infections are limited. Favorable clinical responses have been cited with tigecycline (alone or in combination with colistin) in some patients with MDR-ABC infections,\textsuperscript{1,196} but large, randomized trials are lacking. In one retrospective study, 266 patients with XDR-ABC infections treated with tigecycline \textit{alone or combined with other agents} (i.e., CP, extended-spectrum CEPH, or piperacillin-tazobactam) were compared with 120 patients who received imipenem plus sulbactam to treat XDR-ABC.\textsuperscript{197} All isolates were resistant to all antibiotics tested except tigecycline and colistin. Thirty-day mortality rates were similar (44.7 and 46.7%) between the groups. A prospective multicenter phase III trial cited lower cure rates in patients with ABC-VAP treated with tigecycline (68% cure) compared with imipenem (78% cure).\textsuperscript{198} Overall mortality rates were similar with tigecycline (14.2%) and imipenem (12.2%). A retrospective study of adults with pneumonia in the ICU due to MDR-ABC matched 84 patients receiving tigecycline to 84 patients receiving colistin.\textsuperscript{199} Mortality was higher (60.7%) among patients receiving tigecycline compared with colistin (44% mortality, \( p = 0.04 \)). This excess mortality was significant only for those with MIC greater than 2 \( \mu \)g/mL.\textsuperscript{199} Ye et al retrospectively analyzed 168 hospitalized ICU patients with pneumonia due to ABC treated with either sulbactam or ampicillin/sulbactam (\( n = 84 \)) to patients treated with tigecycline (\( n = 84 \)).\textsuperscript{200} Clinical responses (66.7% for each group) and mortality rates were similar (17.9% with sulbactam, 25.0% with tigecycline; \( p = 0.26 \)). Microbiological eradication was achieved more often with sulbactam (63.5 vs. 33.3%).

Tigecycline achieves low peak serum concentrations (< 0.8 mg/L) after a standard 100 mg loading dose,\textsuperscript{1} a concentration below the MIC of many ABC isolates. Resistance to tigecycline may develop even while on therapy,\textsuperscript{194} and persistence of infection (with or without resistance) may occur.\textsuperscript{1} Efficacy of tigecycline for BSI due to ABC therefore cannot be assured. Importantly, tigecycline has been associated with an increased risk of death when studied against comparator antibiotics, especially among patients with hospital-acquired pneumonia (HAP).\textsuperscript{201} Higher doses of tigecycline (75–100 mg twice daily) have been recommended by some investigators,\textsuperscript{43} but randomized trials have not been done. Given the aforementioned limitations, we do not recommend tigecycline monotherapy to treat serious ABC infections.

\textbf{Eravacycline}

Eravacycline is a novel fluorocycline of the tetracycline class with broad-spectrum activity against gram-negative and gram-positive aerobic and anaerobic pathogens.\textsuperscript{202} Like tigecycline, eravacycline is not affected by many of the tetracycline-specific resistance mechanisms found in gram-negative bacteria, including acquired efflux systems and ribosomal protection.\textsuperscript{202} Eravacycline is two- to fourfold more active (reduced MIC\textsubscript{90}) than tigecycline versus \textit{A. baumannii}.\textsuperscript{203} Whether this increased in vitro activity translates into greater clinical efficacy is not known.
Other Antimicrobial Agents

**Rifampin**
Rifampin exhibits activity against MDR-ABC in vitro and in animal models. In animal models, the combination of rifampin plus colistin may confer additive or synergic bactericidal activity. However, in two randomized trials of serious MDR-ABC infections, the combination of rifampin plus colistin was no better than colistin alone. The role of rifampin as part of combination therapy has not been established.

Other Combination Therapy Using Colistin
Combination therapy has been studied to treat MDR-ABC, particularly with colistin as part of the combination. In vitro studies have shown that synergy may be achieved with combinations of colistin, carbapenems, and rifampicin, in both colistin-S and colistin-R strains of *Acinetobacter* spp. In a retrospective multicenter study, Batirel et al evaluated 250 BSIs due to extremely drug resistant (XDR)-ABC (all isolates were susceptible to colistin). Groups included colistin monotherapy (*n* = 36); colistin + CP (*n* = 102); colistin + sulbactam (*n* = 69); and colistin + other agents (*n* = 43). Complete response rates, 14-day and in-hospital survival, and microbiologic eradication were significantly higher in the combination group, but no differences could be seen between the various combinations. A multicenter prospective observational study in Spain of 101 patients with MDR-ABC infections demonstrated no significant difference in 30-day mortality between combination therapy with colistin versus monotherapy with various agents, predominantly a CP. Cheng et al prospectively studied 176 episodes of bacteremia due to XDR-*A. baumannii* in three hospitals in Taiwan. Among infections with tigecycline MIC > 2 mg/L, combination therapy with colistin plus tigecycline was associated with significantly higher 14-day mortality and more breakthrough bacteremias compared with colistin plus CP. The addition of glycopeptides (agents with gram-positive activity) to colistin has displayed synergy against ABC in vitro. However, clinical studies are limited, and data are conflicting.

Novel Agents
It is obvious that new agents are needed to treat ABC infections. Anti-GNB compounds that belong to old classes of agents such as β-lactams, CPs, FQs, and β-lactamase inhibitors are in development, as are novel classes. Ceftazidime/avibactam contains an older third-generation CEPH (i.e., ceftazidime), with avibactam, a synthetic non-β-lactam, β-lactamase inhibitor that inhibits the activities of Ambler class A and C β-lactamases and some Ambler class D enzymes. Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime against *Acinetobacter* spp. Ceftolozane is a novel cephalosporin with a chemical structure similar to that of ceftazi-dime, with the exception of a modified side chain at the three-position of the cephem nucleus, which confers potent antipseudomonal activity. The addition of tazobactam extends the activity of ceftolozane to include most ESBL producers as well as some anaerobic species. Limited data suggest that ceftolozane/tazobactam is 8- to 16-fold more active than ceftazidime versus *A. baumannii*. Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Plazomicin is a next-generation aminoglycoside that was synthetically derived from sisomicin. Plazomicin demonstrates activity against both gram-negative and gram-positive bacterial pathogens, including isolates harboring all clinically relevant aminoglycoside-modifying enzymes. Limited data suggest that plazomicin demonstrates approximately eightfold more active than gentamicin versus *A. baumannii*. Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Among the new classes of antimicrobials, bis-indole compounds inhibit DNA and RNA synthesis and some have had very good in vitro activity against MDR ABC. Applying structure-based drug design, pyrrolopyrimidine agents were developed that inhibit both of the bacterial topoisomerases (DNA gyrase and topoisomerase IV) of GNB including ABC, *Pseudomonas aeruginosa*, and *E. coli*. Antimicrobial peptides, naturally occurring molecules of the innate immune systems of all types of living organisms, are potential new treatments for MDR organisms. Some of these, including mellitin, indolicidin, and mastoparan, exhibit activity against colistin-susceptible and colistin-resistant ABC isolates in vitro.

Prevention
Hospital outbreaks of *Acinetobacter* infections may reflect environmental contamination or carriage of *A. baumannii* on the hands of health care workers. Aggressive infection-control measures including identifying sources of transmission, environmental cleaning, contact precautions, and hand hygiene and isolating or cohorting infected and colonized patients may be critical to stop or prevent outbreaks. In one study, daily chlorhexidine baths in ICU patients reduced the development VAP due to *Acinetobacter*.

Conclusion
The dramatic global rise of antimicrobial resistance among ABCs reflects acquisition of novel resistance elements and spread via a few international clones. Many isolates are resistant to all antimicrobials except colistin, and some infections are untreatable with existing agents. Novel approaches including combinations of agents and extended infusion times may be required to optimize therapy. Appropriate use of antimicrobials and infection-control measures are critical to minimize antimicrobial resistance.
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