Resistant Gram-Negative Infections

Henry Fraimow, MD[a,*], Raquel Nahra, MD[b]

KEYWORDS

• Enterobacteriaceae • *Pseudomonas aeruginosa* • *Acinetobacter* species
• Gram-negative bacilli • Septic shock • Antibiotic resistance

KEY POINTS

- Worldwide increased incidence of multidrug-resistant gram-negative bacilli (GNB) has been associated with worse outcomes.
- Strategies including combination therapy and extended antimicrobial infusion are increasingly being used in attempts to treat these infections.
- Source control remains an important part of managing septic shock as clinicians are faced with increasing incidence of multidrug-resistant GNB, a paucity of new agents, and ineffectiveness of older agents.

BACKGROUND

The global crisis in antimicrobial resistance continues to escalate. Infections caused by multidrug-resistant (MDR) gram-negative bacilli (GNB) are particularly challenging, with little immediate help forthcoming in the antimicrobial pipeline.[1–3] The crisis of MDR infections is especially vexing in the intensive care unit (ICU), where the highest rates of MDR GNB are found.[4] In the ICU, early effective antimicrobial therapy improves survival of patients with septic shock and other life-threatening infections, but selective pressures from intense antimicrobial exposure contribute to the emergence of MDR bacteria, including extensively drug-resistant (XDR) and even pan–drug-resistant (PDR) organisms.[5] MDR pathogens colonizing patients in ICUs can "leak" into the long-term patient population and even into the community setting, when former ICU patients cycle through the acute and chronic health care system.

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[a] Department of Medicine, Cooper Medical School of Rowan University, 401 Haddon Avenue, Room 278, Camden, NJ 08103, USA; [b] Department of Medicine, Cooper Medical School of Rowan University, 401 Haddon Avenue, Room 261, Camden, NJ 08103, USA
* Corresponding author.
E-mail address: Fraimow-henry@cooperhealth.edu

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This article reviews the major classes of resistant and MDR GNB and their current prevalence in ICUs worldwide. The authors discuss the older and new drugs of potential use in treating these infections, and current strategies to maximize their effectiveness, including rational combination therapy and dosing schemes optimizing the pharmacodynamics of these agents. Treatment options are presented for specific classes of resistant GNB encountered in the ICU, including extended β-lactamase (ESBL)-producing, AmpC-producing, and carbapenem-resistant Enterobacteriaceae (CRE), MDR and carbapenem-resistant *Acinetobacter baumannii* (ACCB), and MDR *Pseudomonas aeruginosa* (PA).

EPIDEMIOLOGY

Antimicrobial resistance is a major public health catastrophe. Following the introduction of each new antimicrobial, reports of resistance rapidly appear. In the late 1970s, reports described mechanisms of resistance of GNB to aminoglycoside and the newly introduced cefamandole.[6] More recently, the lag from introduction of new agents to reports of resistance has markedly decreased, with resistance often identified even before release of the drug. A wide variety of resistance mechanisms are described in GNB. Some mechanisms, such as ESBL production, are found in many species. Others are highly specific, such as overexpression of the MexAB-OprM efflux pump in PA.[7] GNB resistance mechanisms are reviewed elsewhere.[8,9] Important classes of resistance are summarized in **Table 1**.

The trend toward increased resistance among GNB is reported in numerous local, regional and international studies. Recent data from a few of these studies are shown in **Table 2**. In the United States, 10-year surveillance from the Tracking Resistance in the United States Today (TRUST) study describes the steady increase in resistant and MDR GNB isolated in 26 institutions.[10] For example, imipenem-resistant PA increased from 5% in 2003 to 15% in 2009. The prevalence of ESBL-producing *Escherichia coli* increased from 20.8% to 65 % over 7 years among intra-abdominal infection isolates in China.[11] This trend toward increased resistance has been especially significant in ICUs in both tertiary care centers and community hospitals worldwide.[12,13] ACCB are particularly problematic, with resistance rates of up to 60% to 70% in international studies.[11,14] Studies also demonstrate that colonization with MDR GNB is a risk for subsequent infections and bacteremia with same organism.[15] The US Centers for Disease Control and Prevention (CDC) is currently performing population-based surveillance of infection caused by CRE and MDR ACCB through the Multi-Site Resistant Gram-Negative Bacilli Surveillance Initiative (MuGSI), with data expected in 2013.[16] The goals of this project are to determine the extent of CRE and MDR ACCB infections in the United States, identify those most at risk for infection, and measure trends of disease over time.

DEFINITIONS AND DIAGNOSIS OF INFECTIONS CAUSED BY RESISTANT AND MDR GNB

Until recently there was little consensus on the definitions of MDR, XDR, and PDR.[17–22] To remedy the issue, an expert panel sponsored by CDC and the European Center for Disease Prevention and Control (ECDC) met in 2008 to establish interim standard definitions for MDR, XDR, and PDR for epidemiologically significant microorganisms, as well as to begin to establish consistency in categorization of “susceptible” and “nonsusceptible” for different organisms and antimicrobial classes.[23] These definitions were developed specifically for public health and epidemiology purposes and not for clinical management. An organism was designated as nonsusceptible to an antibiotic when it tested intermediate or resistant when using clinical breakpoints as interpretive criteria.

Table 1
Definitions of multidrug resistance and predominant mechanisms of resistance to traditional gram-negative antibiotics

	Common Resistance Phenotypes	Major Mechanisms of Resistance
Enterobacteriaceae	Third- ± fourth-generation cephalosporins	ESBL, AmpC β-lactamases
	Carbapenem resistance	Carbapenemases
	Fluoroquinolones	DNA gyrase and topoisomerase mutations
	Aminoglycosides	Aminoglycoside-modifying enzymes
Pseudomonas aeruginosa	Carbapenem resistance and other β-lactam resistance	Metallo-β-lactamases AmpC and other β-lactamases Multidrug efflux pumps Deletion of membrane porins
	Fluoroquinolones	DNA gyrase and topoisomerase mutations
	Aminoglycosides	Aminoglycoside-modifying enzymes
Acinetobacter spp	Cephalosporin and carbapenem resistance	Cephalosporinases Carbapenemases Multidrug efflux pumps Porin mutations Penicillin-binding protein changes
	Aminoglycoside resistance	Aminoglycoside-modifying enzymes
	Fluoroquinolone resistance	DNA gyrase and topoisomerase mutations
Resistance category definitions	MDR is defined as resistant to more than 1 agent in 3 or more antimicrobial categories XDR is defined as nonsusceptible to more than 1 agent in all but 2 categories PDR is defined as resistant to all categories Intrinsic resistance to specific antimicrobial agent would automatically eliminate that agent from being included in defining resistance	

Only acquired resistance was considered, thus intrinsic species-wide resistance to specific antimicrobial agents was not considered in defining classes of resistance. MDR is defined as nonsusceptible to more than 1 agent from 3 or more antimicrobial categories, XDR is defined as nonsusceptible to more than 1 agent in all but 2 categories, and PDR is defined as resistant to all categories. The antimicrobial categories and breakpoints for determining nonsusceptibility are individually defined for each clinically significant class of GNB (ie, Enterobacteriaceae, PA, and ACCB) (**Table 3**).

Epidemiologic definitions used for nonsusceptibility are not always concordant with outcome data from treating infections attributable to nonsusceptible organisms. For some drug-organism combinations, minimum inhibitory concentration (MIC) values are shown to be more predictive of clinical outcome than characterization as susceptible, intermediate, or resistant by MIC. For most GNB, the Clinical Laboratory and Standards Institute (CLSI) have recently reduced the MIC breakpoint for susceptibility to most cephalosporins and carbapenems to 1 μg/mL or less, based on clinical outcome data (see **Table 3**).[24] However, patients with GNB bloodstream infections nonsusceptible to a carbapenems with a MIC of 2 μg/mL or less were more likely to have a good outcome than those with a MIC of 4 μg/mL or greater.[25] Conversely, for

Table 2
Representative global surveillance data for resistant gram-negative bacilli

Study	Location	Site of Isolation	No. of Isolates (Gram-Negative)	Isolates	Surveillance Period
Tracking Resistance in the United States (TRUST) Surveillance	USA	Not specified	EN (35,847) PA (8882) AC (1621)	ESBL EC: 1% (2003) to 3.5% (2009) ESBL KP: 4% (2003) to 5.8% (2009) EN MDR[a]: 7.5% (1999) to 12.3% (2009) PA MDR[a]: 7.3% (1999) to 7.7% (2009) AC MDR[a]: 24.7% (1999) to 43.6%(2009)	1999–2009
Study for Monitoring Antimicrobial Resistance Trends (SMART) Surveillance Program	Canada/Rest of World	Urine Intra-abdominal infections	Canada: 936 Rest of world: 19,276	ESBL EC: 8%[b]; 21%[c] ESBL *Klebsiella* spp: 6%[b], 33%[c]	2002–2010
SMART Surveillance (China)	China	Intra-abdominal infections	3420 EC ESBL+ 882 KP ESBL+ 193 PA 286 AC 154	ESBL EC 20.8% (2002) to 64.9% (2009) ESBL KP 24% (2002) to 31.9% (2009) PA 80% retained susceptibility to AG AC <30% susceptibility to all agents	2002–2009
MDR GNR reported to the National Healthcare Safety Network	USA	Sputum Blood Urine Surgical site	15,275 isolates PA 7092 AC 2068 KP 6115	KP 15% resistant to 3 antimicrobial classes and 7% resistant to 4 antimicrobial classes PA 10% resistant to 3 antimicrobial classes and 2% resistant to 4 antimicrobial classes ACCB 60% resistant to 3 antimicrobial classes and 34% resistant to 4 antimicrobial classes	2006–2008

CAN-ICU	Canada ICU	Sputum Blood Wound/tissue Urine	EC 536 KP 224 PA 419	FQ-resistant EC 21% MDR EC 0.2% MDR PA 12.6%	2005–2006
International Nosocomial Infection Control Consortium (INICC) Report	422 ICUs in 36 countries in Central and South America, Asia, South Asia, Oceania, Europe, North Africa, and the Middle East	Urine Sputum Blood Other	PA 589 tested for piperacillin susceptibility 517 tested for imipenem susceptibility KP 447 tested for ceftriaxone/ceftazidime susceptibility 508 tested for carbapenem susceptibility AC 667 tested for carbapenem susceptibility EC 171 tested for ceftriaxone/ceftazidime susceptibility 182 tested for imipenem/meropenem/ertapenem susceptibility 133 tested for fluoroquinolone susceptibility	Data below are reported as % of strains resistant PA Fluoroquinolone 42.1% Piperacillin/tazobactam 36% Amikacin 27.7% Imipenem or Meropenem 47.2% Cefepime100% KP Ceftriaxone/ceftazidime 76.3% Imipenem/meropenem/ertapenem 7.9% AC Imipenem/meropenem 55.3% EC Ceftriaxone/ceftazidime 66.7% Imipenem/meropenem/ertapenem 4.4% Fluoroquinolone 53.4%	2004–2009

Abbreviations: AC, *Acinetobacter* spp; EC, *E coli*; EN, Enterobacteriaceae; KP, *K pneumoniae*; PA, *P aeruginosa*.

[a] MDR (Defined as resistant to $\geq$3 antibiotic classes).

[b] Canada isolates.

[c] Rest of the world.

Data from Refs.[10–14,106]

Table 3
Breakpoints for susceptibility as approved by EUCAST, SCLIS, and FDA (in μg/mL)

	EUCAST Cefepime/			CLSI Cefepime/			FDA Cefepime/		
	Imipenem/ Tobramycin			Imipenem/ Tobramycin			Imipenem/ Tobramycin		
Enterobacteriaceae	≤1	≤2	≤2	≤2	≤1	≤4	≤8	≤4	≤4
Pseudomonas aeruginosa	≤8	≤4	≤4	≤8	≤2	≤4	≤8	≤4	≤4
Acinetobacter spp	—	≤2	≤4	≤8	≤4	≤4	≤8	≤4	≤4

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, The European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration.

levofloxacin, patients with GNB bacteremia in whom levofloxacin MIC was 1 μg/mL, well below the susceptibility cutoff, had poorer outcomes than those with MICs of 0.5 μg/mL or less.[26] The conclusion to be drawn from these data is that breakpoints for susceptibility need to be continually reassessed based on clinical outcomes for emerging resistances. However, there may still be reasons for using agents that test as nonsusceptible for the treatment of resistant organisms.

MANAGEMENT OF INFECTIONS CAUSED BY RESISTANT GNB

The cornerstone of treating of resistant gram-negative infections is administration of maximally effective antimicrobial therapy. Whether this can be accomplished depends on several key factors including host status, the type of resistance(s) encountered and available treatment options, the site(s) of infection, and whether source control of infection is achievable. Many resistant GNB infections are treatable with available gram-negative agents such as third- and fourth-generation cephalosporins, β-lactam/β-lactamase inhibitor (BL/BI) agents, carbapenems, or fluoroquinolones. However, some MDR infections are only treatable with more toxic agents including polymyxins and aminoglycosides.[27,28] Treatment of XDR and PDR organisms may require combinations of partially active or individually inactive agents. Optimizing pharmacodynamics of available agents by use of extended infusion times and novel delivery methods including aerosolization may also improve outcomes for marginally treatable infections.[29–31] PDR infections for which there are no available effective treatments are increasingly reported.[1,2] This discussion focuses on treatment of documented resistant GNB infections, but similar principles apply to empiric therapy for severe infections in individuals at high risk for resistant GNB, including colonized patients or patients in an outbreak setting.

ANTIMICROBIAL AGENTS FOR INFECTIONS CAUSED BY MDR GNB

There are often many options for treating resistant GNB with single-class antimicrobial resistance. Rarely, however, do resistant GNB demonstrate single-class resistance. Multidrug resistance is selected by sequential exposures to different antibiotics, by horizontal transfer of multiple resistance traits clustered on mobile genetic elements, or by selection for characteristics such as permeability changes or upregulation of efflux pumps that alter susceptibility to multiple drug classes.[8] Knowledge of local susceptibility patterns from current antibiograms, especially unit-specific antibiograms, may help guide initial therapy. Combination antibiograms demonstrating patterns of cross-resistance may be even more useful for this.[32] Standard broad-spectrum gram-negative agents including third- and fourth-generation cephalosporins,

carbapenems, BL/BI agents, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole may be effective against some MDR GNB, especially ESBL-producing and AmpC-expressing strains. This section focuses on newer agents and some older agents with particular activity, used alone or in combination against resistant GNB (**Table 4**).

Recently Approved Agents: Doripenem and Tigecycline

There have been only 3 agents with broad-spectrum gram-negative activity approved by the US Food and Drug Administration since 2005. Ceftaroline, a novel fifth-generation cephalosporin, has enhanced gram-positive/methicillin-resistant *Staphylococcus aureus* activity, and offers little new for resistant GNB. Doripenem is a newer carbapenem with a spectrum similar to that of imipenem and meropenem. Some isolates, especially PA, with low-level resistance to imipenem and meropenem via permeability or efflux remain susceptible to doripenem.[33] Doripenem is hydrolyzed by *Klebsiella pneumoniae* carbapenemases (KPCs) and metallo-β-lactamases (MBLs), and is not significantly more active alone than other carbapenems for CRE or carbapenem-resistant (CR) ACCB.[9] Doripenem has good stability in solution, and is thus well suited for extended interval infusions.[33] Doripenem was more active in in vitro combinations than other carbapenems for some XDR and PDR strains, although the clinical significance of this is unknown.[34]

Another recently approved agent is tigecycline, a glycylcycline tetracycline analogue with broad-spectrum activity first introduced in the United States in 2005. Tigecycline has activity against most Enterobacteriaceae and ACCB. PA and also *Proteus*, *Morganella*, and *Providencia* spp are intrinsically resistant via efflux pumps, and acquired tigecycline resistance is reported in other GNB via enhanced expression of multidrug efflux systems.[27,35] Emergence of resistance on therapy can occur during treatment of CRE and ACCB.[27] Recent large surveys show no significant worsening resistance trends among Enterobacteriaceae including ICU strains, although increased resistance among ACCB is reported.[36] Tigecycline achieves low levels in serum and only 20% is excreted in urine, and is a poor monotherapy agent for MDR GNB bloodstream or urinary tract infections (UTIs) at standard doses.[37] Higher doses of 100 mg every 12 hours have been used for MDR bloodstream infections.[27,37]

Older Agents Active Against MDR, XDR, and PDR GNB

Fosfomycin is an older broad-spectrum antibiotic widely used outside of the United States that inhibits phosphoenolpyruvate, an early step in peptidoglycan synthesis.[38] Oral and parenteral formulations are available in some European and Asian countries, although only oral fosfomycin is available in the United States for treating cystitis. The oral prodrug has good oral bioavailability and achieves high urine levels, although serum levels are low.[38] Fosfomycin has broad activity against Enterobacteriaceae including most *E coli* and *Klebsiella* strains. Some PA are susceptible, although not ACCB. There is no cross-resistance with other agents, and fosfomycin remains active against many MDR CRE. The primary niche for fosfomycin is treatment of MDR GNB UTIs, but there are reports from Europe on the use of parenteral fosfomycin for systemic infections. Fosfomycin is used in combination therapy to prevent emergence of resistance.[39] There are only limited data on outcome or emergence of resistance in these settings.[39]

Of the older tetracyclines, minocycline maintains the best activity against ACCB.[40] Like tigecycline, minocycline is a poor substrate for most tetracycline-resistance efflux pumps in GNB. The intravenous formulation is widely available in Europe and Asia, and since 2009 has also been available in the United States. Minocycline may be active against sulbactam-resistant and carbapenem-resistant ACCB strains, and even some

tigecycline-resistant strains, and has been used for the treatment of a variety of complicated ACCB infections, including ventilator-associated pneumonia (VAP), although experience remains limited.[41]

The β-lactamase inhibitor sulbactam binds to ACCB penicillin-binding protein PBP-2, and has specific potent inhibitory activity against many ACCB.[42] In most countries sulbactam is only available as a coformulation with ampicillin. Rates of ampicillin-sulbactam resistance are increasing among ACCB, especially CR ACCB.[27,43] Sulbactam has been studied in vitro combined with carbapenems, and this regimen has been used clinically for treatment of XDR and PDR ACCB.[43]

Aztreonam, a monobactam, is a substrate for most broad-spectrum β-lactamases including ESBL, AmpC, and KPC. However, aztreonam is uniquely resistant to hydrolysis by some MBLs including New Delhi MBL-1.[44] Aztreonam may have a role in infections caused by MBL-producing CRE, and some isolates are susceptible. However, most strains carry multiple β-lactamases in addition to the MBLs, so aztreonam needs to be combined with other agents. Combinations of aztreonam and other monobactams with novel β-lactamase inhibitors are being evaluated.

Rifampin is a potent, bactericidal broad-spectrum antimicrobial that inhibits DNA-dependent RNA polymerase. Primarily an antimycobacterial drug, rifampin is used in combination therapy for gram-positive infections but is increasingly used for MDR and XDR GNB. Rifampin has relatively poor activity against most GNB because of its poor outer membrane penetration, and resistance is easily selected in vivo when used as monotherapy. Rifampin combinations have been extensively studied in vitro, particularly rifampin plus polymyxins and/or carbapenems for CRE, MDR, ACCB, and PA.[45] These studies demonstrate potent synergy between rifampin and other agents.[45] Rifampin may delay the emergence of resistance to other agents in vitro, especially to polymyxins. Synergy may result in increased rifampin access to intracellular targets in the presence of cell membrane–damaging agents, even in some polymyxin-resistant isolates (**Fig. 1**).

Off of the Antibiotic Scrap Heap: the Resurrection of the Polymyxins

Polymyxins are cationic polypeptide antibiotics that bind to lipopolysaccharide (LPS) in gram-negative outer membranes and to cytoplasmic membranes, resulting in altered permeability and cell death. Polymyxins were introduced in the 1950s for the treatment of GNB, but owing to toxicity concerns virtually disappeared after the introduction of broad-spectrum β-lactams.[27,46] Polymyxins were "rediscovered" in the 1990s for the treatment of MDR GNB. Polymyxins have broad activity against many GNB including *E coli, Klebsiella*, *Enterobacter*, PA, and ACCB, although several important pathogens, notably *Proteus*, *Providencia*, and most *Serratia*, are intrinsically resistant. Because of the unique mechanism of action, there is no cross-resistance with other agents. Resistance to polymyxins is uncommon, but may occur by modification of LPS outer-membrane target components, including lipid A.[46–48] Colistin resistance is increasingly reported in ACCB.[48]

The available polymyxins are colistin (polymyxin E), which is more widely used in the United States, and polymyxin B. Colistin is administered as the inactive prodrug colistimethate sodium (CMS), which is converted in vivo to the active colistin sulfate; polymyxin B is administered as the active sulfate moiety. Polymyxins appear to have relatively poor distribution into lung tissue, pleural fluid, and cerebrospinal fluid (CSF). A recent multicenter study sponsored by the National Institutes of Health has led to new proposed guidelines for dosing CMS, including administration of a loading dose.[49] CMS is also administered by aerosol therapy for resistant respiratory tract infections.[31] Susceptibility testing for polymyxins remains problematic. Disc-diffusion

testing is highly unreliable in comparison with Etests or other MIC methods. The limiting toxicity of colistin is nephrotoxicity.[46,47] Reported rates in recent series range from as low as 6% to as high as 32% to 55% in other studies in critically ill patients.[46] Definitions of nephrotoxicity and dosing regimens varied in these studies. Most nephrotoxicity is reversible.

Gram-Negative Agents on the Horizon

Despite the overall lack of new drug classes and paucity of new gram-negative agents in the antibiotic pipeline, there are several agents currently in phase 1 or phase 2 trials that may improve the treatment of resistant GNB.[50] These agents include several novel β-lactamase inhibitors with activity against KPC enzymes, although not against MBLs. One of these, avibactam (formerly NXL-104), is in trials in combination with several β-lactams. BLI-489, another novel inhibitor, is entering clinical trials. BAL30376 is a monobactam–clavulanic acid combination drug with specific activity against MBLs. New aminoglycosides such as plazomicin, which are stable to common gram-negative aminoglycoside-modifying enzymes, are also under study. Other agents with novel mechanisms of activity against GNB are in early phases of development.[27,50]

EVIDENCE FOR EFFECTIVENESS OF TREATMENT OF MDR, XDR, AND PDR GNB

Ample evidence exists from in vitro susceptibility data, pharmacokinetic and pharmacodynamic modeling, and clinical outcome data to make recommendations for the treatment of infections caused by ESBL and AmpC GNB (**Table 5**). The evidence for treatment of more resistant pathogens, including CRE, MDR and PDR PA, and ACCB is less robust. Combination therapy may be assessed in vitro by synergy testing in checkerboard and time-kill assays. Polymyxins are challenging to study in the laboratory because of binding of drug to surfaces and other poorly understood in vitro phenomena. Pharmacodynamic models are extensively used to optimize dosing regimens for organisms with borderline susceptibility. A few drug combinations have been tested in animal models. However, the pool of experimental data is small, the clinical correlates of in vitro testing are uncertain, and the limited number of strains studied may not adequately represent the diversity of MDR and XDR clinical isolates.

Human treatment data most often consist of case reports or uncontrolled case series, making comparison of different regimens difficult. There are a small number of well-conducted nonrandomized studies with case-control designs, and there have been several recent systematic reviews focusing on specific pathogens or the effectiveness of specific drugs.[39,51] Randomized clinical trials comparing monotherapy and combination regimens for MDR and XDR infections are currently enrolling subjects in Europe and the United States, although recruitment is challenging.[52,53]

OPTIMIZING THE USE OF AVAILABLE AGENTS TO TREAT MDR GNB

Extended Infusion of β-Lactams for MDR GNB

The most important pharmacodynamic parameter for killing by β-lactams is the time above the MIC of the target organism. This criterion is the theoretical basis for extended-infusion or continuous-infusion β-lactam strategies for treating GNB (**Fig. 2**).[29,54] Some agents (eg, imipenem) are not suitable for extended infusion owing to their poor stability in solution. Most experience with extended-interval dosing is with piperacillin-tazobactam, which is increasingly used in such a manner for both efficacy and economic considerations.[55] Experience is also increasing with doripenem and meropenem, and with cephalosporins including ceftazidime and cefepime. Initial

Table 4
Some new and older antimicrobials with activity against multidrug-resistant gram-negative bacilli

Antimicrobial Agent	Drug Class/Mechanism	Formulations	Standard and Maximal Dosing	MDR GNB Activity	Comments
Doripenem	Carbapenem	Intravenous	500 mg every 8 h Maximum: 1000 mg every 8 h	ESBL AmpC CS ACCB CS PA	Active against some imipenem- or meropenem-resistant PA Used in combination therapy for CR ACCB, CR PA, and CRE Extended-infusion time dosing
Tigecycline	Tetracycline	Intravenous	100 mg load then 50 mg every 12 h Maximum: 100 mg every 12 h	ESBL AmpC CRE MDR ACCB	Low serum and urine levels Breakthrough bacteremias while on therapy Used as monotherapy or combination therapy
Fosfomycin	Phosphoenolpyruvate inhibitor	Oral Parenteral (in some countries)	Oral (for UTI): 3 g every 48–72 h Intravenous: 2–4 g every 6 h	ESBL AmpC CRE PA	High urine levels Resistance develops while on therapy Only as combination therapy for systemic infections
Sulbactam	β-Lactam inhibitor with β-lactam activity	Intravenous (as ampicillin-sulbactam)	1 g every 4 h (3 g ampicillin-sulbactam every 4 h)	ACCB only	Used as monotherapy for susceptible ACCB. Used in combination therapy for sulbactam-resistant ACCB

Aztreonam	Monobactam	Intravenous	2 g every 8 h	NDM-producing CRE	Must be used in combination to overcome other resistances
Rifampin	RNA polymerase inhibitor	Oral Intravenous	Oral and intravenous: 600 mg every 24 h Maximum: 600 mg every 8 h	CRE MDR ACCB MDR PA	Only used in combination therapy Synergy with polymyxins Resistance emerges on therapy
Minocycline	Tetracycline	Intravenous Oral	Oral and Intravenous: 100 mg every 12 h	MDR ACCB	Used as monotherapy or combination therapy
Polymyxins (colistin, polymyxin B)	Cationic polypeptide Damages lipid membranes	Parenteral Aerosolized Intrathecal	See **Table 6** for dosing information	CRE MDR ACCB MDR PA	Active against *E coli, Klebsiella*, *Enterobacter*, PA, ACCB Significant nephrotoxicity Synergy with many other agents, even against colistin-resistant strains

Abbreviations: CS, carbapenem-sensitive; NDM, New Delhi metallo-β-lactamase.

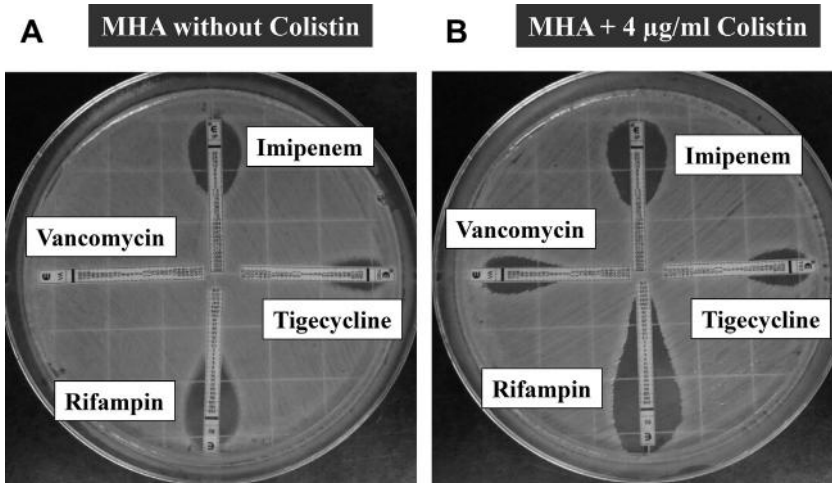

Fig. 1. Demonstration of synergy of other antibiotics with colistin for a carbapenem-resistant and colistin-resistant ACCB strain. Susceptibility to vancomycin, rifampin, tigecycline and imipenem was determined by Etest on plates without (*A*) or with (*B*) addition of 4 μg/ml of colistin. Susceptibility to vancomycin and rifampin was dramatically increased and susceptibility to tigecycline and imipenem was modestly increased in presence of colistin. (*Courtesy of* C. Knob.)

randomized controlled trials failed to demonstrate significant differences in outcome in comparison with standard administration.[30,54]

However, patients in these trials may not have been "sick" enough or infected with resistant enough GNB to show benefits of improved attainment of pharmacodynamics targets. In one study, superiority of extended piperacillin-tazobactam infusion was limited to only the sickest patients.[56] A recent systematic review and meta-analysis of predominantly nonrandomized trials showed benefit with extended or continuous infusion of pipericillin-tazobactam or carbapenems in patients with all sites of infection, and specifically those with pneumonia.[30] A recent small, randomized trial of continuous infusion of piperacillin-tazobactam, meropenem, and ticarcillin–clavulanic acid in 5 ICUs demonstrated both better drug levels and cure rates.[57] With limited options in critically ill patients with borderline or low-level resistant organisms, extended infusion is a rational strategy. Extended infusion of antibiotics demonstrating concentration-dependent killing, such as aminoglycosides, is not indicated. Colistin has been administered by continuous infusion, but pharmacokinetic and safety data do not currently support such dosing strategies.

Aerosolized Aminoglycosides and Polymyxins for Respiratory Infections

Aerosolized administration provides benefits of enhanced delivery to epithelial lining fluid (ELF) for drugs that have poor pulmonary penetration or significant toxicity with systemic dosing. Aerosolized therapy is used for preventing or treating respiratory infections in patients with cystic fibrosis and bronchiectasis, and has been studied for the treatment of VAP. Use in the ICU has increased with the increase in VAP caused by MDR GNB.[31] Most experience is with aminoglycosides and polymyxins, agents with potent in vitro gram-negative activity but with significant systemic toxicity and poor lung penetration.[31]

There are several recent studies of aerosolized aminoglycoside therapy for VAP, but only one small randomized study comparing aerosolized with intravenous therapy.[58]

Two larger retrospective observational studies compared benefits of aerosolized therapy added to intravenous therapy that included many MDR pathogens. Reported cure rates were 59% and 73%.[59,60] Gentamicin and tobramycin doses are 300 mg every 12 hours, and amikacin doses are 500 to 1000 mg every 12 hours. Treatment has been generally well tolerated.

There are multiple reports of treating VAP caused by resistant ACCB and PA with aerosolized colistin, with overall reported cure rates of 58% to 100%.[31] Use of concurrent systemic therapy and choice of systemic agents varied in these trials. One well-designed retrospective case-control study for VAP comparing intravenous plus aerosolized colistin with intravenous therapy alone demonstrated a trend toward better outcomes and lower mortality in the aerosol-treated group.[61] Respiratory symptoms are more frequently reported with aerosolized colistin than with aminoglycosides, and drug preparation in accordance with standard protocols is important to prevent toxicity.[31] The recommended dose of colistin is 150 mg every 12 hours.[31]

Definitive recommendations for the use of aerosolized aminoglycosides or polymyxins in addition to systemic drug, or in combination with other agents, are lacking. Aerosolized regimens should be considered in patients failing or relapsing after systemic treatment, and for MDR infections with limited treatment options. Systemic therapy is still necessary when treating concurrent bacteremia or other sites of infection outside the respiratory tract.

RECOMMENDATIONS FOR THE TREATMENT OF SPECIFIC CLASSES OF RESISTANT GNB

ESBL-Producing Enterobacteriaceae

There are numerous case series assessing treatment of ESBLs, but no randomized, comparative trials. Options also depend on the site and severity of infection, the specific ESBL enzyme, and additional associated resistances (see **Table 5**). For ESBL bacteremia, most expert opinion and a recent meta-analysis support using a carbapenem.[62–65] Carbapenems are highly active in vitro, stable to hydrolysis by ESBLs, and do not demonstrate an inoculum effect (decreased in vitro activity with large bacterial concentrations), and there is extensive clinical experience. Experience with the narrower-spectrum drug ertapenem for ESBL infections for bacteremia is less than for other carbapenems.[66] Piperacillin-tazobactam has been used for bloodstream and urinary tract ESBL infections, and in a recent meta-analysis was not inferior to carbapenems for bacteremia caused by susceptible isolates.[65,67]

Recommendations regarding cephalosporins for ESBL Enterobacteriaceae have changed following revision of the CLSI susceptibility breakpoints in 2010.[24] These new lower breakpoints eliminate the broad characterization of ESBL strains as pan-cephalosporin resistant, and support treatment with third- or fourth-generation cephalosporins when MICs are 1 μg/mL or less, regardless of the presence of ESBL enzymes. Some cephalosporins are more stable to hydrolysis by specific ESBL enzymes, and demonstrate good outcomes for treating ESBLs when MICs are in these lower ranges. In one study, 11 of 12 patients with ESBL-producing *K pneumoniae* and *E coli* infections with MICs to cefepime of 2 μg/mL or less had cure or improvement.[68] Good outcomes were also reported with ceftazidime for cefotaxime-resistant but ceftazidime-susceptible ESBL *E coli* bacteremia.[69] When using cefepime for bacteremia and pneumonia caused by susceptible ESBL strains, maximal doses may be necessary.[70]

There is limited information on the use of fluoroquinolones or aminoglycosides for serious ESBL infections. Fluoroquinolone resistance rates are high, and even if quinolone susceptible, the outcome of patients with bacteremia treated with fluoroquinolones is poorer than with a carbapenem.[71] Resistance can also be selected in vivo,

Table 5
Options for treatment of different classes of multidrug-resistant gram-negative bacilli

Resistance Class	Site of Infection	Preferred Option	Alternatives	Comments
ESBL	Bacteremia and pneumonia	Carbapenem	Third-/fourth-generation cephalosporin if MIC $\leq$1 Piperacillin-tazobactam	
	Urine and other low-severity, low-inoculum infections		Fluoroquinolone Aminoglycoside Trimethoprim-sulfamethoxazole Fosfomycin	
AmpC	Bacteremia and pneumonia	Carbapenem or cefepime	Piperacillin-tazobactam Fluoroquinolone	Resistance to third-generation cephalosporin develops on therapy
	Urine and other low-severity, low-inoculum infections		Third-generation cephalosporin Aminoglycoside Trimethoprim-sulfamethoxazole	
CRE	Bacteremia	Colistin[a]	Tigecycline Carbapenem (if MIC $\leq$4) Only in combination therapy: Rifampin Fosfomycin Aztreonam (for NDM strains)	If susceptible can use: Aminoglycoside Fluoroquinolone Trimethoprim-sulfamethoxazole Usually combination therapy Combination therapy usually includes 2–3 drugs
ACCB	All sites	Carbapenem	Sulbactam Colistin Tigecycline	Sulbactam may be equivalent to carbapenem

CR ACCB and pan-resistant ACCB	Bacteremia		If Susceptible: Sulbactam Colistin[a] Tigecycline In combination only: Rifampin	Combination therapy commonly used
	Pneumonia		Systemic therapy plus aerosolized aminoglycoside or colistin	
MDR PA	Bacteremia		Colistin[a] Aminoglycosides If susceptible: Doripenem For combination therapy only: Rifampin Fosfomycin	Combination therapy if possible for bacteremia Susceptibilities vary: some isolates remain susceptible to ceftazidime, cefepime, piperacillin-tazobactam, or aztreonam
	Pneumonia		Systemic therapy plus aerosolized aminoglycoside or colistin	
	UTI only		Fosfomycin	
Stenotrophomonas maltophilia	Pneumonia and bacteremia	Trimethoprim-sulfamethoxazole	Ticarcillin–clavulanic acid Fluoroquinolone	Levofloxacin and moxifloxacin more active than ciprofloxacin

[a] Colistin or polymyxin B.

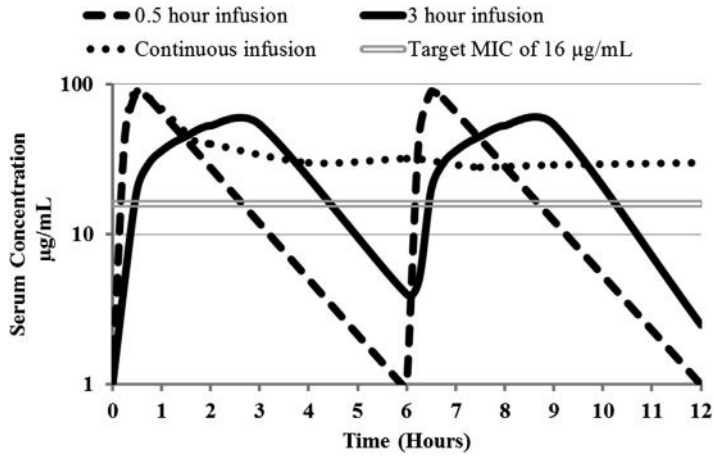

Fig. 2. Pharmacokinetics of standard-, prolonged-, and continuous-infusion β-lactam regimens. The graph shows the representative pharmacokinetics of a standard dose of β-lactam with a short half-life such as piperacillin-tazobactam when administered by 0.5-hour infusion (*dashed line*) or by a 3-hour infusion (*solid line*) every 6 hours. When treating an organism with a higher minimum inhibitory concentration (MIC) of 16 μg/mL, the time that drug concentration is above the MIC is increased using the prolonged infusion time. Administration of a standard bolus dose followed by continuous infusion of drug can theoretically provide even greater time above the MIC (*dotted line*).

especially in higher inoculum infections. Treatment failures with aminoglycosides have also been reported.[72] For nonbacteremic infections, especially those with low bacterial inoculum and lower potential for emergence of resistance, fluoroquinolones and aminoglycosides may be appropriate. Trimethoprim-sulfamethoxazole is also an option for susceptible isolates, especially UTIs.[64] Cephamycins, including cefoxitin, are not inactivated by ESBLs and are active in vitro, but because resistance can develop by other mechanisms, these are poor choices for serious infections.[64] Fosfomycin is active against most ESBL *E coli* and *Klebsiella* isolates, and is an option for UTIs.[38,39]

AmpC-Producing Enterobacteriaceae

Up to 20% of AmpC-producing *Enterobacter cloacae* may fail therapy with a third-generation cephalosporin during treatment of bacteremia, owing to emergence of resistance.[73,74] Use of these agents is not recommended for serious infections caused by AmpC-expressing GNB, especially bacteremia, pneumonia, and intra-abdominal infections.[74] Carbapenems and cefepime are not readily hydrolyzed by AmpC and are treatments of choice. Rare strains are resistant to carbapenems or cefepime because of altered permeability or expression of additional β-lactamases. Resistance is less likely to develop to piperacillin-tazobactam than to third-generation cephalosporins. Fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole are acceptable options for susceptible strains.

Carbapenem-Resistant Enterobacteriaceae

Recommendations for the treatment of CRE are based on in vitro data and published experience from case reports, retrospective reviews, small case series, and recent systematic reviews.[75] Most data concern the treatment of KPC- or MBL-expressing CR *Klebsiella*. In recent studies, other variables that affect the outcome of CRE

infections include site of infection and carbapenem MIC, as well as host factors such as age, underlying comorbidities, severity of illness, and being in an ICU.[75,76] Treatment options are limited by the high rates of resistance to other drug classes, including resistance to fluoroquinolone, aminoglycoside, and trimethoprim-sulfamethoxazole. Ninety percent to 100% of isolates may be fluoroquinolone resistant. Rates of pan-aminoglycoside resistance are variable especially for KPC strains, and aminoglycosides have been used alone or in combination.[77] CRE treatment regimens can be broadly characterized as monotherapy, generally with either a carbapenem, colistin, aminoglycoside, or tigecycline; or combinations that include colistin and/or a carbapenem.[75] Other components of combinations often include tigecycline or rifampin. Comparison of different regimens is difficult because of patient diversity and variable CRE susceptibility patterns. One recent review has attempted to compare the outcome of various regimens.[75] Although there are limitations to this analysis, there were some interesting observations. Ineffective therapy resulted in worse outcomes. Carbapenem-based combination regimens were among the most effective despite carbapenem nonsusceptibility, and carbapenem monotherapy was superior to no effective therapy. Effectiveness of carbapenems correlated with MIC, with some successes with monotherapy for strains having MICs as high as 8 μg/mL.[78] Despite reported susceptibility to tigecycline of most CRE, failure rates may be higher than for other monotherapy regimens, with reports of breakthrough bacteremia.[37,75] Higher tigecycline doses of 100 mg every 12 hours are recommended for bacteremic infections.[75]

Polymyxins are increasingly being used for the treatment of CRE, with more published data for colistin than for polymyxin B. Ninety percent to 100% of KPC-producing or MBL-producing *K pneumoniae* were reported as susceptible to polymyxins, but colistin-resistant strains are increasingly being described.[79]

Reported outcomes with colistin monotherapy vary greatly, in part likely because of nonstandardized colistin dosing. Routine use of more uniform, data-driven dosing regimens (**Table 6**), including an initial loading dose rapidly achieving levels above the MIC, may provide better comparative data on colistin effectiveness.[49]

Table 6
Colistin dosing

Intravenous loading dose	T × 2 × body weight Not to exceed 300 mg First maintenance dose in 24 h
Intravenous maintenance dose	T × ((1.5 × creatinine clearance) + 30) Interval based on creatinine clearance <10 mL/min/1.73 m^2: interval every 12 h 10–70 mL/min/1.73 m^2: interval every 12–8 h >70 mL/min/1.73 m^2: interval every 8 h Intermittent hemodialysis (HD): On non-HD days supplement with 30 mg of colistin On HD days infuse after HD 39 mg of colistin every 12 h Continuous hemofiltration: 192 mg every 8–12 h
Inhaled	150 mg every 12 h
Intrathecal	10–20 mg qd

T is defined as desired plasma colistin, which varies by MIC, organ, and severity of infection.

Data from Drusano GL, Lodise TP. Editorial commentary: saving lives with optimal antimicrobial chemotherapy. Clin Infect Dis 2013;56:245–7; and Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. Clin Microbiol Infect 2008;14:816–27.

Combination regimens, including some drugs that individually test as intermediate or resistant, are increasingly being used for CRE, especially XDR and PDR strains.[75] Regimens consist of at least 2 to 3 drugs from a menu including polymyxins, tigecycline, rifampin, carbapenems, and aminoglycosides. Assumptions of synergy are extrapolated from published experimental data rather than direct testing of clinical isolates, as few institutions have the ability to perform real-time in vitro synergy studies. In one in vitro study, polymyxin B plus rifampin was synergistic for 15 of 16 KPC *K pneumoniae*, including 2 polymyxin-resistant isolates.[80] Similar results were seen for 12 of 12 polymyxin-resistant KPC strains.[81] A double carbapenem regimen of ertapenem plus doripenem also showed activity in vitro.[82] There are numerous reports for other combinations as well.[75] Comparative outcome data for different regimens is lacking. Aerosolized aminoglycosides or colistin can be used for the treatment of CRE pneumonia, usually in combination with systemic therapy.[31]

MDR, XDR, and Pan-Resistant Acinetobacter baumannii

ACCB strains possess numerous intrinsic resistances, and readily assimilate and express new resistance mechanisms. MDR ACCB are important nosocomial pathogens, especially for VAP but also for traumatic wound infections, UTIs, and meningitis.[42] Previously considered a low-virulence, opportunistic pathogen, more recent studies demonstrate the morbidity attributable to ACCB infections, as well as the benefits of appropriate antibiotic therapy in improving survival in critically ill ICU patients with ACCB bacteremia.[42,43,83] Drugs used for the treatment of MDR ACCB alone or in combination include carbapenems, sulbactam (available as ampicillin-sulbactam), tigecycline, minocycline, aminoglycosides, rifampin, and polymyxins (see **Table 5**). Occasional isolates remain susceptible to fluoroquinolone or trimethoprim-sulfamethoxazole. Carbapenems are drugs of choice for ACCB, but rates of CR ACCB have increased over the past decade.[36,43,84,85] Carbapenem resistance is mediated by several classes of carbapenemases, most prominently the oxacillinase (OXA) and MBL enzymes; effects of carbapenemases are augmented by changes in outer membrane protein and multidrug efflux pumps. Unlike other GNB, ACCB may display differential susceptibilities for imipenem and meropenem.[43] Doripenem is not significantly more active than other carbapenems.[86] For ACCB with higher carbapenems MICs, higher doses and extended-interval dosing with meropenem (2 g every 8 hours) or doripenem (up to 1 g every 8 hours) may provide a pharmacodynamic advantage.[27] Sulbactam is active against many ACCB strains. In one study, outcomes for ACCB were better with ampicillin-sulbactam than with a carbapenem.[42] High total daily sulbactam doses of 6 g (18 g ampicillin-sulbactam) were used for bacteremia and meningitis. Sulbactam resistance is increasing.[43] A combination of a carbapenem and sulbactam was reported to be effective in 4 patients with sulbactam-resistant CR ACCB.[87]

Of other agents employed for CR ACCB, polymyxins maintain the highest susceptibility rates and are the most extensively studied.[27,36,43] Colistin monotherapy was equivalent to a carbapenem for the treatment of ACCB pneumonia, and a recent meta-analysis of 6 ACCB pneumonia studies suggested that colistin monotherapy was as effective as comparators, without evidence of higher toxicity.[51,88] For CR ACCB, colistin combined with carbapenems, rifampin, tetracyclines, macrolides, and even glycopeptides have been studied in vitro and in animal models for.[27,43,89–91] Colistin resistant strains may be hypersusceptible to non–gram-negative antibiotics, possibly because of enhanced outer membrane permeability (see **Fig. 2**).[90] There are only limited outcome data comparing colistin monotherapy with combination therapy. One retrospective study showed no benefit of colistin plus meropenem versus

colistin alone for MDR infections.[17] Intravenous colistin has been combined with aerosolized colistin for treating MDR ACCB pneumonias.[31,61]

The tetracyclines tigecycline and minocycline are options for the treatment of CR ACCB infections, including colistin-resistant strains, although rates of tigecycline resistance are increasing.[36,40,43] Success rates for tigecycline monotherapy or combination therapy for nosocomial ACCB pneumonia are reported to be as high as 75%, although outcomes for bacteremia are worse.[43,92] Tigecycline doses of 100 mg every 12 hours have been used to optimize serum levels.[37,43] Susceptibility rates for minocycline are similar to those for tigecycline, and intravenous minocycline is now available in the United States. In vitro studies show synergy with minocycline and colistin and carbapenems, even against isolates resistant to some of these agents, although experience with minocycline for serious ACCB infections is limited.[41]

Treatment of nosocomial meningitis caused by ACCB, especially CR ACCB, is especially challenging. Sulbactam at maximal doses may not achieve adequate CSF levels. Colistin has been administered intrathecally, either alone or with systemic therapy, and appears to be well tolerated.[93]

MDR and XDR Pseudomonas aeruginosa

PA remains an important pathogen in the ICU. Like ACCB, PA expresses many antimicrobial resistances and demonstrates propensity to develop resistance while on therapy, although PA is a more virulent pathogen. PA is a major cause of health care–associated pneumonia and VAP, but is important in other settings, including neutropenic and burn patients, injection drug users, and patients with cystic fibrosis and chronic lung diseases. Although an MDR phenotype is less prevalent among PA than in ACCB, MDR PA infections, particularly respiratory infections and bacteremia, are extremely challenging and have high mortality.[94] Increasing rates of MDR PA are reported in surveys of ICUs internationally.[13,95]

PA express β-lactam resistance through expression of multiple β-lactamases including AmpC, MBLs, KPCs, and OXA enzymes, as well as by efflux pumps and changes in outer membrane permeability. Unlike in most CRE and CR ACCB, carbapenem resistance does not indicate broad resistance to all β-lactams or even resistance to all carbapenems, especially for resistance mediated primarily by permeability changes and not carbapenemases. For example, doripenem may be active against OprD outer membrane mutants with a low level of imipenem resistance, but imipenem and doripenem may be active against strains with efflux-mediated resistance to meropenem.[96] Susceptibility to cefepime, ceftazidime, or piperacillin-tazobactam may be preserved despite carbapenem resistance. However, PA strains susceptible to β-lactams such as piperacillin-tazobactam often have MICs near susceptibility breakpoints with a higher likelihood of emergence of resistance on therapy, thus use of maximal daily doses and extended-interval infusions may be appropriate.[56]

PA may remain susceptible to some aminoglycosides; tobramycin and amikacin are usually the most active. Aminoglycoside monotherapy is not recommended for most serious PA infections, especially pneumonia or bacteremia, but options for agents to combine with an aminoglycoside may be limited with concurrent β-lactam and quinolone resistance. Aerosolized aminoglycosides have been used for treatment of VAP caused by MDR PA.[31,59] Aerosolized therapy may be especially useful in cases where risks of toxicity of systemic aminoglycosides are high or where MICs are higher than levels achievable with systemic therapy.

Polymyxins remain active in vitro against most PA strains in recent surveys, although there are reports of resistance emerging on therapy.[97–99] Clinical experience with polymyxins for PA bacteremia is limited. Monotherapy has been effective in some

patients but is inferior to β-lactam therapy.[98] Recent trials of aerosolized colistin have included VAP patients with MDR PA, with favorable reported outcomes.[31,61] Susceptible PA infections are commonly treated with combination therapy, most often with a β-lactam plus an aminoglycoside, although the benefits of this strategy remain controversial.[100] There are few clinical data available on combination therapy for MDR and XDR PA strains. There are in vitro data for colistin plus doripenem, or with rifampin for MDR and XDR PA.[34] Colistin-aminoglycoside combinations would be predicted to have high rates of nephrotoxicity. Parenteral fosfomycin remains an alternative for use in combination therapy for systemic MDR PA infections.[101]

MDR Stenotrophomonas maltophilia

Stenotrophomonas maltophilia (SM) is a low-virulence but highly resistant GNB that colonizes patients and occasionally causes respiratory infections in ICUs. SM is resistant to carbapenems and usually most other β-lactams, as well as aminoglycosides.[102] Trimethoprim-sulfamethoxazole is active against nearly all strains, and is the treatment of choice.[19,102] Ticarcillin-clavulanate may be effective, even for isolates resistant to all other β-lactams, and fluoroquinolones are also an alternative for susceptible isolates.[103] Unlike for most GNB, levofloxacin and moxifloxacin are more active than ciprofloxacin against SM in vitro. Tigecycline and minocycline also have excellent in vitro activity.[103]

ADJUVANT THERAPY FOR MDR INFECTIONS: SOURCE CONTROL AND INFECTION PREVENTION

With increasing drug resistance and few new antibiotics available, a crucial component of management of infections caused by MDR pathogens is source control. Source control is critical to the management of septic shock and severe sepsis.[104,105] Though not specifically studied for less severe MDR infections, prompt removal of infected venous catheters and devices, drainage of infected collections, and debridement of infected soft tissue are efficacious ways to decrease the bacterial burden and limit the development of even further resistance to the few useful drugs available. Surveillance and infection-prevention strategies are beyond the scope of this review but are also a critical component in identifying and limiting the spread of MDR infections in the ICU setting.

SUMMARY

MDR gram-negative infections are increasingly prevalent in ICUs worldwide, and therapeutic options are limited. Antibiotic choices vary with class of resistance. For the most resistant organisms such as CRE and MDR ACCB, treatment may include polymyxins and other older drugs, newer drugs such as tigecycline, and multidrug combinations. Current evidence for combinations is limited. Source control is also critical in the management of MDR infection.

REFERENCES

1. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1–12.
2. Livermore DM. Has the era of untreatable infections arrived? J Antimicrob Chemother 2009;64(Suppl 1):i29–36.
3. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155–64.

4. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Ann Intensive Care 2011;1:47.
5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.
6. Rosenthal SL, Freundlich LF, Quraishi MA. Sensitivity of gentamicin-resistant Enterobacteriaceae to cefamandole and cefoxitin. Chemotherapy 1979;25(3): 157–62.
7. Koch DC, Raunest M, Harder T, et al. Unilateral access regulation: ground state dynamics of the *Pseudomonas aeruginosa* outer membrane efflux duct OprM. Biochemistry 2013;52(1):178–87.
8. Fraimow HS, Tsigrelis C. Antimicrobial resistance in the intensive care unit: mechanisms, epidemiology, and management of specific resistant pathogens. Crit Care Clin 2011;27:163–205.
9. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. Mayo Clin Proc 2011;86:250–9.
10. Pillar CM, Brown NP, Sahm DF, et al. Trends towards increased resistance among clinically important gram-negative pathogens in the US; results from 10 years of TRUST surveillance (1999-2009). Abstract C2-696, Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston (MA): 2010. Available at: http://www.eurofins.com/media/1770121/C2-696.pdf. Accessed January 23, 2013.
11. Yang Q, Wang H, Chen M, et al. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002-2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2010;36:507–12.
12. Kallen AJ, Hidron AI, Patel J, et al. Multidrug resistance among gram-negative pathogens that caused healthcare-associated infections reported to the National Healthcare Safety Network, 2006-2008. Infect Control Hosp Epidemiol 2010;31:528–31.
13. Zhanel GG, DeCorby M, Laing N, et al. Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. Antimicrob Agents Chemother 2008; 52:1430–7.
14. Rosenthal VD, Bijie H, Maki DG, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. Am J Infect Control 2012;40:396–407.
15. Borer A, Saidel-Odes L, Eskira S, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospitalized patients initially only colonized with carbapenem resistant *K. pneumoniae*. Am J Infect Control 2012;40:421–5.
16. Available at: http://www.cdc.gov/hai/eip/mugsi_techinfo.html. Accessed January 23, 2013.
17. Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. J Med Microbiol 2006;55:1619–29.
18. Goossens H. Susceptibility of multi-drug-resistant *Pseudomonas aeruginosa* in intensive care units: results from the European MYSTIC study group. Clin Microbiol Infect 2003;9:980–3.

19. Falagas ME, Karageorgopoulos DE. Pandrug resistance (PDR), extensive drug resistance (XDR), and multidrug resistance (MDR) among gram-negative bacilli: need for international harmonization in terminology. Clin Infect Dis 2008;46:1121–2.
20. Apisarnthanarak A, Pinitchai U, Thongphubeth K, et al. A multifaceted intervention to reduce pandrug-resistant *Acinetobacter baumannii* colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study. Clin Infect Dis 2008;47:760–7.
21. Doi Y, Husain S, Potoski BA, et al. Extensively drug-resistant *Acinetobacter baumannii*. Emerg Infect Dis 2009;15:980–2.
22. Park YK, Peck KR, Cheong HS, et al. Extreme drug resistance in *Acinetobacter baumannii* infections in intensive care units, South Korea. Emerg Infect Dis 2009;15:1325–7.
23. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–81.
24. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twentieth informational supplement CLSI document M100-S20. Wayne (PA): Clinical and Laboratory Standards Institute.
25. Esterly JS, Wagner J, McLaughlin MM, et al. Evaluation of clinical outcomes in patients with bloodstream infections due to Gram-negative bacteria according to carbapenem MIC stratification. Antimicrob Agents Chemother 2012;56(9): 4885–90.
26. Defife R, Scheetz MH, Feinglass JM, et al. Effect of differences in MIC values on clinical outcomes in patients with bloodstream infections caused by gram-negative organisms treated with levofloxacin. Antimicrob Agents Chemother 2009;53(3):1074–9.
27. Kosmidis C, Poulakou G, Markogiannakis A. Treatment options for infections caused by carbapenem-resistant gram negative bacteria. Eur Infect Dis 2012; 6:28–34.
28. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. Crit Care Clin 2008;24:377–91.
29. Drusano GL, Lodise TP. Editorial commentary: saving lives with optimal antimicrobial chemotherapy. Clin Infect Dis 2013;56:245–7.
30. Falagas ME, Tansarli GS, Ikawa K, et al. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and Piperacillin/Tazobactam: a systematic review and meta-analysis. Clin Infect Dis 2013; 56:272–82.
31. Wood GC. Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. Expert Rev Anti Infect Ther 2011;9:993–1000.
32. Beardsley JR, Williamson JC, Johnson JW, et al. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Chest 2006;130:787–93.
33. Mandell L. Doripenem: a new carbapenem in the treatment of nosocomial infection. Clin Infect Dis 2009;49(Suppl 1):S1–3.
34. Urban C, Mariano N, Rahal JJ. In vitro double and triple bactericidal activities of doripenem, polymyxin B, and rifampin against multidrug-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Escherichia coli*. Antimicrob Agents Chemother 2010;54:2732–4.
35. Livermore DM. Tigecycline: what is it, and where should it be used? J Antimicrob Chemother 2005;56:611–4.

36. Wang YF, Dowzicky MJ. In vitro activity of tigecycline and comparators on *Acinetobacter* spp. isolates collected from patients with bacteremia and MIC change during the Tigecycline Evaluation and Surveillance Trial, 2004 to 2008. Diagn Microbiol Infect Dis 2010;68:73–9.
37. Burkhardt O, Rauch K, Kaever V, et al. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. Int J Antimicrob Agents 2009;34:101–2.
38. Raz R. Fosfomycin: an old–new antibiotic. Clin Microbiol Infect 2012;18:4–7.
39. Falagas ME, Kastoris AC, Kapaskelis AM, et al. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis 2010;10: 43–50.
40. Arroyo LA, Mateos I, Gonzalez V, et al. In vitro activities of tigecycline, minocycline, and colistin-tigecycline combination against multi- and pandrug-resistant clinical isolates of *Acinetobacter baumannii* group. Antimicrob Agents Chemother 2009;53:1295–6.
41. Jankowski CA, Balada-Liasat J. A stewardship approach to combating multidrug-resistant *Acinetobacter* infections with minocycline. Infect Dis Clin Pract (Baltim Md) 2012;20:184–7.
42. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538–82.
43. Fishbain J, Peleg AY. Treatment of *Acinetobacter* infections. Clin Infect Dis 2010; 51:79–84.
44. Shakil S, Azhar EI, Tabrez S, et al. New Delhi metallo-beta-lactamase (NDM-1): an update. J Chemother 2011;23:263–5.
45. Drapeau CM, Grilli E, Petrosillo N. Rifampicin combined regimens for gram-negative infections: data from the literature. Int J Antimicrob Agents 2010;35: 39–44.
46. Yahav D, Farbman L, Leibovici L, et al. Colistin: new lessons on an old antibiotic. Clin Microbiol Infect 2012;18:18–29.
47. Nation RL, Li J. Colistin in the 21st century. Curr Opin Infect Dis 2009;22:535–43.
48. Cai Y, Chai D, Wang R, et al. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 2012;67:1607–15.
49. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011;55:3284–94.
50. Freire-Moran L, Aronsson B, Manz C, et al. Critical shortage of new antibiotics in development against multidrug-resistant bacteria—time to react is now. Drug Resist Updat 2011;14:118–24.
51. Florescu DF, Qiu F, McCartan MA, et al. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. Clin Infect Dis 2012;54:670–80.
52. Trial for the treatment of extensively drug-resistant gram-negative bacilli. Available at: http://clinicaltrials.gov/ct2/show/NCT01597973. Accessed January 24, 2013.
53. Multicenter open-label randomized controlled trial (RCT) to compare colistin alone versus colistin plus meropenem. Available at: http://clinicaltrials.gov/ct2/show/NCT01732250. Accessed January 24, 2013.
54. Abdul-Aziz MH, Dulhunty JM, Bellomo R, et al. Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care 2012;2:37.

55. George JM, Colton BJ, Rodvold KA. National survey on continuous and extended infusions of antibiotics. Am J Health Syst Pharm 2012;69:1895–904.
56. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007;44:357–63.
57. Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 2013;56:236–44.
58. Hallal A, Cohn SM, Namias N, et al. Aerosolized tobramycin in the treatment of ventilator-associated pneumonia: a pilot study. Surg Infect (Larchmt) 2007;8: 73–82.
59. Czosnowski QA, Wood GC, Magnotti LJ, et al. Adjunctive aerosolized antibiotics for treatment of ventilator-associated pneumonia. Pharmacotherapy 2009;29: 1054–60.
60. Mohr AM, Sifri ZC, Horng HS, et al. Use of aerosolized aminoglycosides in the treatment of Gram-negative ventilator-associated pneumonia. Surg Infect (Larchmt) 2007;8:349–57.
61. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. Clin Infect Dis 2010;51: 1238–44.
62. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis 2004;39:31–7.
63. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med 2010;362:1804–13.
64. Pitout JD. Infections with extended-spectrum beta-lactamase-producing Enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs 2010;70:313–33.
65. Vardakas KZ, Tansarli GS, Rafailidis PI, et al. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother 2012;67:2793–803.
66. Lye DC, Wijaya L, Chan J, et al. Ertapenem for treatment of extended-spectrum beta-lactamase-producing and multidrug-resistant gram-negative bacteraemia. Ann Acad Med Singapore 2008;37:831–4.
67. Gavin PJ, Suseno MT, Thomson RB Jr, et al. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin- tazobactam against extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella* species. Antimicrob Agents Chemother 2006;50:2244–7.
68. Labombardi VJ, Rojtman A, Tran K. Use of cefepime for the treatment of infections caused by extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. Diagn Microbiol Infect Dis 2006;56:313–5.
69. Bin C, Hui W, Renyuan Z, et al. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing *Escherichia coli*. Diagn Microbiol Infect Dis 2006;56:351–7.
70. Lee NY, Lee CC, Huang WH, et al. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis 2013;56:488–95.
71. Endimiani A, Luzzaro F, Perilli M, et al. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment

outcome of patients receiving imipenem or ciprofloxacin. Clin Infect Dis 2004; 38:243–51.
72. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. Antimicrob Agents Chemother 2002;46:1481–91.
73. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991; 115:585–90.
74. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev 2009;22:161–82.
75. Tzouvelekis LS, Markogiannakis A, Psichogiou M, et al. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev 2012;25:682–707.
76. Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. Clin Microbiol Infect 2012;18: 54–60.
77. Souli M, Galani I, Antoniadou A, et al. An outbreak of infection due to beta-Lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. Clin Infect Dis 2010;50:364–73.
78. Daikos GL, Markogiannakis A. Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems? Clin Microbiol Infect 2011;17:1135–41.
79. Elemam A, Rahimian J, Mandell W. Infection with panresistant *Klebsiella pneumoniae*: a report of 2 cases and a brief review of the literature. Clin Infect Dis 2009;49:271–4.
80. Bratu S, Tolaney P, Karumudi U, et al. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. J Antimicrob Chemother 2005;56:128–32.
81. Elemam A, Rahimian J, Doymaz M. In vitro evaluation of antibiotic synergy for polymyxin B-resistant carbapenemase-producing *Klebsiella pneumoniae*. J Clin Microbiol 2010;48:3558–62.
82. Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2011;55: 3002–4.
83. Lee YT, Kuo SC, Yang SP, et al. Impact of appropriate antimicrobial therapy on mortality associated with *Acinetobacter baumannii* bacteremia: relation to severity of infection. Clin Infect Dis 2012;55:209–15.
84. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006-09). J Antimicrob Chemother 2011;66:2070–4.
85. Manchanda V, Sanchaita S, Singh N. Multidrug resistant *Acinetobacter*. J Glob Infect Dis 2010;2:291–304.
86. Paterson DL, Depestel DD. Doripenem. Clin Infect Dis 2009;49:291–8.
87. Lee NY, Wang CL, Chuang YC, et al. Combination carbapenem-sulbactam therapy for critically ill patients with multidrug-resistant *Acinetobacter baumannii* bacteremia: four case reports and an in vitro combination synergy study. Pharmacotherapy 2007;27:1506–11.
88. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia

(VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111–8.
89. Bassetti M, Repetto E, Righi E, et al. Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections. J Antimicrob Chemother 2008;61:417–20.
90. Gordon NC, Png K, Wareham DW. Potent synergy and sustained bactericidal activity of a vancomycin-colistin combination versus multidrug-resistant strains of *Acinetobacter baumannii*. Antimicrob Agents Chemother 2010;54:5316–22.
91. Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. Clin Microbiol Infect 2008;14:816–27.
92. Poulakou G, Kontopidou FV, Paramythiotou E, et al. Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. J Infect 2009; 58:273–84.
93. Cascio A, Conti A, Sinardi L, et al. Post-neurosurgical multidrug-resistant *Acinetobacter baumannii* meningitis successfully treated with intrathecal colistin. A new case and a systematic review of the literature. Int J Infect Dis 2010;14:e572–9.
94. Tam VH, Rogers CA, Chang KT, et al. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. Antimicrob Agents Chemother 2010;54:3717–22.
95. Croughs PD, Li B, Hoogkamp-Korstanje JA, et al. Thirteen years of antibiotic susceptibility surveillance of *Pseudomonas aeruginosa* from intensive care units and urology services in the Netherlands. Eur J Clin Microbiol Infect Dis 2012; 32(2):283–8.
96. Riera E, Cabot G, Mulet X, et al. *Pseudomonas aeruginosa* carbapenem resistance mechanisms in Spain: impact on the activity of imipenem, meropenem and doripenem. J Antimicrob Chemother 2011;66:2022–7.
97. Durakovic N, Radojcic V, Boban A, et al. Efficacy and safety of colistin in the treatment of infections caused by multidrug-resistant *Pseudomonas aeruginosa* in patients with hematologic malignancy: a matched pair analysis. Intern Med 2011;50:1009–13.
98. Kvitko CH, Rigatto MH, Moro AL, et al. Polymyxin B versus other antimicrobials for the treatment of *Pseudomonas aeruginosa* bacteraemia. J Antimicrob Chemother 2011;66:175–9.
99. Lee JY, Song JH, Ko KS. Identification of nonclonal *Pseudomonas aeruginosa* isolates with reduced colistin susceptibility in Korea. Microb Drug Resist 2011;17:299–304.
100. Chamot E, Boffi El Amari E, Rohner P, et al. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2003;47:2756–64.
101. Apisarnthanarak A, Mundy LM. Use of high-dose 4-hour infusion of doripenem, in combination with fosfomycin, for treatment of carbapenem-resistant *Pseudomonas aeruginosa* pneumonia. Clin Infect Dis 2010;51:1352–4.
102. Nicodemo AC, Paez JI. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. Eur J Clin Microbiol Infect Dis 2007;26:229–37.
103. Insa R, Cercenado E, Goyanes MJ, et al. In vitro activity of tigecycline against clinical isolates of *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. J Antimicrob Chemother 2007;59:583–5.
104. Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med 2004;32:S513–26.

105. Sulaiman L, Hunter J, Farquharson F, et al. Mechanical thrombectomy of an infected deep venous thrombosis: a novel technique of source control in sepsis. Br J Anaesth 2011;106:65–8.
106. Rennie RP, Turnbull L, Johnson A. Surveillance of gram-negative intra-abdominal and urinary tract pathogens in Canada compared to the rest of the world: the SMART study Abstract C2-1789, Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago (IL): 2011.