MDR Gram-negative Pathogens

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LEARNING OBJECTIVES

1. Evaluate for the presence of gram-negative bacteria along with their corresponding resistance using novel diagnostic techniques.
2. Design an optimal treatment plan for Enterobacteriales infections based on patient-specific characteristics and antimicrobial resistance potential.
3. Design an optimal treatment plan for *Pseudomonas aeruginosa* infections based on patient-specific characteristics and antimicrobial resistance potential.
4. Design an optimal treatment plan for *Acinetobacter* infections based on patient-specific characteristics and antimicrobial resistance potential.
5. Design an optimal treatment plan for *Stenotrophomonas* infections based on patient-specific characteristics and antimicrobial resistance potential.
6. Develop an optimal treatment plan for multidrug-resistant gram-negative infections based on patient-specific characteristics and alternative dosing techniques.

ABBREVIATIONS IN THIS CHAPTER

CRE	Carbapenem-resistant Enterobacterales
DTR	Difficult-to-treat resistance
ESBL	Extended-spectrum β-lactamase
HAI	Healthcare-associated infections
MALDI-TOF	Matrix assisted laser desorption/ionization time-of-flight mass spectrometry
MDR	Multidrug resistant
RDT	Rapid diagnostic testing

Table of other common abbreviations.

INTRODUCTION

Recent Trends

The CDC defines *multidrug-resistant infection* as an infection caused by bacteria with non-susceptibility to at least one antibiotic in at least three of the following classes: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, or carbapenems (Sievert 2019). In examining rates of reported pathogens across all types of adult healthcare-associated infections (HAIs) within the 2015–2017 National Healthcare Safety Network database, *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* were ranked first, third, and fourth, respectively, on the most often reported pathogens (Weiner-Lastinger 2020). They were also the top three most often reported pathogen for adult catheter-associated UTI (Weiner-Lastinger 2020). For adult ventilator-associated pneumonia, *P. aeruginosa*, *Klebesiella* spp., and *Enterobacter* spp. ranked second, third, and fourth, respectively, on the most often reported pathogens (Weiner-Lastinger 2020). For adult HAIs in the hospital wards, 14% of the *P. aeruginosa* isolates, 16% of the *Klebsiella* spp. isolates and 35% of the *Acinetobacter* spp. isolates were resistant to at least 3 antibiotic classes whereas the rates for the ICU were 19%, 20%, and 47%, respectively (Weiner-Lastinger 2020).

Increase in hospital stay, previous antibiotic exposure, and duration of mechanical ventilation are all associated with the increased occurrence of antibiotic resistance (Hyllienmark 2012). Other risk factors for multidrug-resistant (MDR) organisms include advanced age, chronic illness, recent hospital or healthcare exposure, previous surgical intervention, immune suppression, recent antibiotic

use history, and use of external devices, such as endotracheal tubes, intravenous catheters, urinary catheters, and feeding tubes (Morris 2020; Cucci 2019). In examining rates of extended-spectrum β-lactamase (ESBL)-producing versus non-ESBL *Klebsiella* spp., exposure to fluoroquinolones and β-lactam/β-lactamase inhibitor combinations were associated with subsequent growth of ESBL-producing *Klebsiella* spp. (Wener 2010). Previous treatment with fluoroquinolones or extended-spectrum cephalosporins, use of carbapenems, severity of illness, and ICU admission were all associated with the development of carbapenem-resistant *Klebsiella pneumonia* infections (Gasnik 2009; Hussein 2009). The 30-day mortality risk attributed to HAIs with a MDR gram-negative pathogen has been reported to be higher (RR 2.32; 95% CI, 1.85–2.92) and also for specific MDR organisms, such as *Acinetobacter* (RR 3.34; 95% CI, 1.97-5.06), *P. aeruginosa* (RR 2.08; 95% CI, 1.22–3.56), and Enterobacteriaceae (RR 2.07; 95% CI, 1.64–2.60) (Nelson 2017).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of gram-negative resistance
- General knowledge of diagnostic techniques available for identifying pathogens
- General knowledge of antibiotic resistance
- The various antibiotic used to treat infections caused by gram-negative organisms

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Alekshun MN, Levy SB. Molecular mechanism of antibacterial multidrug resistance. Cell 2007; 128:1037-50.
- Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century—a clinical super challenge. N Engl J Med 2009;360:439-43.
- Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum ß-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. Mayo Clin Proc 2011;86:250-9.
- Siegel JD, Rhinehart E, Jackson M, et al. Management of multidrug-resistant organisms in healthcare settings. Atlanta, GA: CDC, 2006.
- Tamma PD, Aitken SL, Bonomo RA, et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0: A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, and Pseudomonas aeruginosa with Difficult-to-Treat Resistance. Clin Infect Dis 2021;2:e169-83.
- Tamma PD, Aitken SL, Bonomo RA, et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0: A focus on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis 2022;74: 2089-114.

Novel Diagnostic Techniques

Phenotypic identification has relied on the use of direct bacterial culture (i.e., agar or broth microdilution, disk diffusion, Etest) and biochemical testing, which has been the standard in identifying the specific pathogens causing infections as well as the subsequent elucidation of the antibiotic resistance pattern. The use of rapid diagnostic testing (RDT) has decreased the time to results, and RDT has the ability to identify organisms that are non-culturable, can identify potential pathogens in culture-negative patients given antibiotics that can inhibit or suppress growth, and can also improve sensitivity (Goldenberg 2021). Some of these RDTs include molecular-based methods of nucleic acid amplification (real-time and multiplex PCR, peptide nucleic acid fluorescence in situ hybridization), and mass spectrometry (matrix assisted laser desorption/ionization time-of-flight mass spectrometry).

Rapid diagnostic testing has become a key factor in the ability to reduce the time to appropriate antibiotics, to reduce duration of unnecessary antibiotic use, and to allow practitioners to make informed decisions on antibiotic de-escalation and discontinuation, as shown in Table 1 (Goff 2017; Review on Antimicrobial Resistance 2015). One of the major goals of the 2020 National Action Plan for Combating Antibiotic-Resistant Bacteria is to advance the development and use of rapid and innovative diagnostic test for identification and characterization of resistant bacteria (U.S. HHS 2020). Tools for RDT are also recommended by WHO to guide antibiotic use in human as well as in veterinary medicine during daily clinical, pharmacy, and veterinary practices (WHO 2015). In addition, the Antibacterial Resistance Leadership Group has advocated for the use of the diagnostic tests that can rapidly detect or exclude bacterial infection, accurately identify bacterial pathogens, and inform selection of antimicrobial agents (Tsalik 2017).

The use of rapid multiplex PCR (matrix assisted laser desorption/ionization time-of-flight mass spectrometry with FilmArray Blood Identification Panel, BioFire Diagnostics, Salt Lake City, UT) has been shown to shorten time to organism identification (1.3 vs. 22.3 hours, p<0.001) as well as time on broad-spectrum antibiotics (44 vs. 56 hours; p=0.01) and

Table 1. Rapid Diagnostic Tests

Technology	Example (Manufacturer)	Considerations
PNA-FISH	Accelerate Pheno (Accelerate Diagnostics) AdvanDX PNA-FISH (OpGen)	• Rapid detection of phenotypic resistance testing with MIC • Identify presence of bacterial genes
Multiplex-PCR	FilmArray Panel (BioFire Diagnostics) Unyvero Panel (Curetis) ePlex Panel (GenMark Diagnostics)	• Detection of vast array of bacteria and fungi • Identify presence of bacterial genes
MALDI-TOF	MALDI-TOF (bioMerieux, Brucker) AccuPRO-ID (Charles River)	• Detection of vast array of bacteria and fungi • Unable to detect resistance mechanism of susceptibility reports
Nanoparticle probe	Verigene (Nanosphere)	• Identify presence of bacterial genes
Nuclear magnetic resonance	T2Bacteria	• Detection of organism without prior isolation • Identify presence of bacterial genes

MALDI-TOF = matrix assisted laser desorption/ionization time-of-flight mass spectrometry; PNA-FISH = peptide nucleic acid fluorescence in situ hybridization.

Information from: Beganovic M, McCreary EK, Mahoney MV, et al. Interplay between rapid diagnostic tests and antimicrobial stewardship programs among patients with bloodstream and other severe infections. J Antibiotic Lab Med 2019;3:601-16.

decreased treatment of contaminants (11% vs. 25%; p=0.015), in addition to identifying common antimicrobial-resistance genes (Banerjee 2015).

Multiple syndromic molecular testing panels, such as the pneumonia panel by BioFire FilmArray and the lower respiratory tract panel by Curetis Unyvero (Holzgerlingen, Germany), have been approved by the FDA in providing rapid identification of potential pathogens and presence of resistance markers from multiple respiratory specimen types, sputum, endotracheal aspirates, and bronchoalveolar lavage fluids, to within 1–5 hours from specimen collection and testing. Compared with the standard conventional microbiological cultures in patients in the ICU, the multiplex PCR assay panel has been shown to have a positive percent agreement of 90% (95% CI, 73.5–97.9%) and negative percent agreement of 97.4% (95% CI, 96.0–98.45) but discrepancies were observed in identifying antibiotic-resistant gene targets (Lee 2019). Another study examining the use of BioFire Pneumonia Panel (BioFire Diagnostics, Salt Lake City, UT) found positive agreement of 94.4% and negative agreement of 96.0% (Gastli 2021). Similarly, the BioFire FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics) showed an 84.4% positive and >99.9% negative agreement between the panel and traditional testing methods (Leber 2016).

Identification of phenotypic antibacterial susceptibility based on a single gene are fairly straightforward, but the presence of resistance determined by multiple genes, mutations, or combination of both are more difficult to identify. Rapid molecular diagnostic platforms (RMDs) that identify the presence or absence of specific genes associated with resistance compared with a reference standard have been used to predict the presence of antimicrobial resistance. In the PRIMERS trials, multiple RMDs were used in *E. coli* and *K. pneumoniae* (PRIMERS I and II), *Acinetobacter* spp. (PRIMERS III), and *P. aeruginosa* (PRIMERS IV) isolates to predict susceptibility and resistance to β-lactam antibiotics (Tsalik 2017).

In addition, testing based on the presence of resistance-determining genes can facilitate rapid administration of appropriate therapy, but it does not provide the MIC for optimal antimicrobial dosing. Automated rapid phenotypic testing systems, such as the Accelerate Pheno System (Tucson, AZ)—which uses peptide nucleic acid fluorescence in situ hybridization together with gel electrofiltration for rapid bacterial identification for targeted gram-negative bacteria, followed by time-lapse microscopy for determining phenotypic antimicrobial susceptibility testing directly from positive blood culture bottles—is able to provide rapid identification within 2 hours and MIC results from positive gram-negative blood cultures within 7 hours of testing. The mean time to results was faster with RAPID than standard-of-care (2.7 vs. 11.7 hours; p<0.001), as was antimicrobial susceptibility testing (2.7 vs. 11.7 hours; p<0.001) and the time to first gram-negative antibiotic modification (17.3 vs. 42.1 hours; p<0.001) (Banerjee 2021). Rapid attainment of MIC allows for optimization of pharmacokinetic and pharmacodynamic targets, which have been associated with improved outcomes (Roberts 2014).

To rapidly identify blood stream infections without prior isolation of the organism, the technology of T2 Magnetic Resonance (T2 Biosystems, Lexington, MA) has been used.

The T2Bacteria panel (T2 Biosystems) can identify infections caused by the five most common ESKAPE organisms—*Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, P. aeruginosa*, and *Enterobacter* spp.—with a sensitivity and specificity of 90% (95% CI, 76%–96%) and 90% (95% CI, 88%–91%), respectively, for proven blood stream infections, whereas the negative predictive value was 99.7% with a 10% false-positive rate (Nguyen 2019). Unfortunately, both the Accelerate Pheno System (Tucson, AZ) and the T2Bacteria systems are currently only available for blood samples.

Integrating RDT with an antimicrobial stewardship program (ASP) has been shown to provide additional benefit beyond just RDT and other ASP interventions, and RDT alone may not be as beneficial without the ASP intervention (Beganovic 2019; Wong 2012). The use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry together with ASP has been shown to decrease the average time to optimal antimicrobial therapy, 30-day mortality, and inpatient mortality in gram-negative bacteremia (Perez 2014). Conversely, the use of RDT enables quicker escalation of antibiotics in the presence of MDR genes or pathogens to ensure appropriate antibiotics. Of note, exclusion of potentially resistant genes and pathogens would only be possible if the RDT contains the gene or pathogen of interest.

To help differentiate between colonization versus true infection as well as viral infections versus bacterial infection, diagnostics based on host response have been used to provide vital information regarding antibiotic duration and potential for colonization. Procalcitonin is a component of the pro-inflammatory response in a bacterial infection that has been used to differentiate between viral and bacterial infections and to minimize antibiotic exposure. The American Thoracic Society/Infectious Diseases Society of America IDSA 2019 community-acquired pneumonia (CAP) guidelines first discussed the use of procalcitonin plus clinical judgment in withholding initiation of antibiotic therapy but recommended antibiotic therapy for patients with clinically suspected and radiographically confirmed CAP regardless of initial serum procalcitonin level (Metlay 2019). A meta-analysis showed the benefit of procalcitonin in reducing antibiotic use and antibiotic-related adverse effects in acute respiratory infections; however, a large study failed to demonstrated such benefit, although it was not paired with antimicrobial stewardship (Huang 2018; Schuetz 2018).

ENTEROBACTERIACEAE

Epidemiology

Enterobacteriaceae encompasses a family of some of the most common pathogens responsible for a wide array of infections, ranging from cystitis to bacteremia to intra-abdominal infections. The most common organisms are *K. pneumoniae, E. coli*, and *Enterobacter* spp., which can be ESBL-producing, especially in patients who have prolonged hospital stays and who have invasive medical devices (Jernigan 2020). The CDC estimates that there are 197,400 hospital- and community-onset cases of ESBL resulting in 9100 deaths in 2019 (Sievert 2019). For adult HAIs on the hospital wards, 25% of the *Klebsiella* spp. isolates were ESBL-resistant Enterobacterales and 8% were carbapenem-resistant Enterobacterales (CRE)-producing (Weiner-Lastinger 2020). The ESBLs are plasmid-mediated, and their potential for transfer of antibiotic-resistant genes creates a challenge for effective control and treatment.

Carbapenem-resistant Enterobacterales is present in 4% of bloodstream infections and 5% of pneumonia cases (Zilberberg 2013). A recent report from the CDC estimated 13,100 hospital- and community-onset cases of CRE, resulting in 1100 deaths in 2019 (Sievert 2019). A systematic review of the epidemiology of CRE reported the incidence ranged from 0.45–4.17 infections per 10,000 patient-days, with higher rates in long-term acute care hospitals (Livorsi 2018). Production of *K. pneumoniae* carbapenemase is especially problematic because it results in decreased susceptibility to virtually all β-lactam antibiotics, in addition to resistance to other classes of antibiotics. Infections with CRE have been associated with increased mortality and an increased odds of being discharged to a long-term acute care facility (Livorsi 2018).

Mechanism of Resistance

Production of β-lactamases is one of the most common mechanisms of resistance in gram-negative bacteria of clinical significance, especially Enterobacterales spp. Classification for β-lactamases is typically based on the functional characteristic of the enzyme (Bush-Jacoby classification) or the protein sequence (Ambler classification), as shown in Table 2. Group 1 cephalosporinases are part of molecular class C, which is present in many Enterobacteriaceae spp., including AmpC-producing spp. Production of AmpC in Enterobacteriaceae typically occurs by inducible chromosomal resistance, such as in *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii,* which are all a moderate to high risk of clinically significant AmpC production, by stable chromosomal de-repression, or by plasmid-mediated *ampC* genes (Tamma 2019).

Group 2 serine β-lactamases are typically divided into many types, as follows: a, b, be, br, bcr, c, ce, d, de, df, e, and f. These β-lactamases include both molecular class A and D, which include most of traditional ESBL enzymes (TEM, SHV, CTX-M, OXA) as well as gram-positive β-lactamases (PCI) (Bush 2010). Typically, ESBL-producing Enterobacterales are the most prevalent, including *E. coli*, *Klebsiella oxytoca,* and *Proteus mirabilis* in the United States, with CTX-M β-lactamase being the most common, followed by TEM and SHV (Tamma 2022a). The CRE are resistant to at least one carbapenem, with *K. pneumoniae*-producing carbapenemases

Table 2. Example of β-Lactamase Enzymes

Bush-Jacoby Group	Ambler Molecular Class	Enzyme Type	Example Enzyme	Common Organisms
1	C	Cephalosporinases	*AmpC*	*Enterobacter* spp. *Citrobacter* spp. *Morganella morganii* *Pseudomonas aeruginosa* *Serratia marcescens*
2a, 2b, 2be, 2c, 3e, 2f	A	Penicillinases	TEM, SHV, SMV, CTX-M, PS, CARB, IMI, KPC	*Escherichia coli* *Klebsiella* spp. *Proteus* spp.
2d	D	Oxacillinases	OXA	*Acinetobacter baumannii* Enterobacteriaceae *Pseudomonas aeruginosa*
3	B	Metallo-β-lactamases	IMP, VIM, NDM, IND, CpthA	*A. baumannii* Enterobacteriaceae *P. aeruginosa*

Information from: Bush K, Jacoby GA. Updated functional classification of β-lactamases. Antimicrobial. Agents Chemother 2010;54:969-76; Hall BG, Barlow M. Revised Ambler classification of β-lactamases. J Antimicrobial Chemother 2005;55;1050-1.

being the most common in United States (Tamma 2022a). The OXA β-lactamases are another type of plasmid-mediated carbapenemase, which originally occurred in *A. baumannii* but transferred to Enterobacteriaceae species (Evans 2014).

Group 3 metallo-β-lactamases are part of molecular class B that includes carbapenemases (IMP, VIM). An example of a metallo-β-lactamases known to be produced by Enterobacteriaceae is NDM-1; other examples are VIMs and IMPs (Tamma 2022a).

Treatment Options

Treatment of resistant Enterobacteriaceae often depends on the specific antibiotic susceptibility for the specific pathogen. Use of cephalosporin as empiric therapy is not reliable for serious ESBL-producing infections because of the potential for resistance, but this approach may be a reasonable option for other Enterobacteriaceae. Although cefotaxime and ceftriaxone are less susceptible to hydrolysis by ESBL than ceftazidime, they are not recommended as empiric therapy for ESBL-producing organisms because of the lack of activity compared with some Enterobacteriaceae or the subsequent induction of β-lactamase production. Some ESBL-producing strains are susceptible to cephamycins (cefoxitin and cefotetan), but resistance can develop during therapy, together with the presence of efflux pumps (Martínez-Martínez 1999). The ESBL strains producing *AmpC* β-lactamases are resistant to cephamycins and to β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, piperacillin/tazobactam and ticarcillin/clavulanate), but they remain susceptible to cefepime and carbapenems. The use of doxycycline for cystitis caused by ESBL-producing species would not be recommended because of limited urinary excretion (Tamma 2022a).

Carbapenems are the agent of choice for serious infections caused by ESBL-producing Enterobacteriaceae. The use of β-lactam/β-lactamase inhibitor combinations such as piperacillin/tazobactam for ESBL is a potential option because of the tazobactam inhibition of some ESBL enzymes, but β-lactam/β-lactamase inhibitor combinations can be susceptible to the inoculum effect, so caution is needed if used for serious infections (Peterson 2008). Fluoroquinolones may also be considered if the isolates are susceptible. Nitrofurantoin and oral fosfomycin can be considered in cystitis, if susceptible, but not in pyelonephritis or complicated UTIs because of inadequate levels achieved. Fosfomycin should also only be considered in uncomplicated cystitis caused by both ESBL and CRE *E. coli* because of the presence of *fosA* gene in gram-negative organisms that can hydrolyze fosfomycin, such as *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens* (Tamma 2022a). The 2022 Infectious Diseases Society of America focused document recommends selection of an agent based on source of infection (cystitis, upper UTI, and infection outside the urinary tract) as well as the potential or presence of resistance (ESBL, CRE) (Tamma 2022a). Similar recommendations by British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party are followed, with slight differences, as indicated in Table 3 (Hawkey 2018).

Cefepime (MIC 2 mcg/mL or less) and carbapenems are recommended in patients when the pathogen is Enterobacterales

Table 3. Treatment Recommendation for Infections Caused by Extended-Spectrum β-Lactamase and CRE Enterobacteriaceae

Infection Source	Preferred Treatment	Alternative Treatment
Extended-Spectrum β-Lactamase		
Cystitis	• Nitrofurantoin • Trimethoprim/sulfamethoxazole	• Amoxicillin/clavulanate • Aminoglycosides x1 dose • Fosfomycin, oral (*E. coli*) • Fluoroquinolones[a] • Ertapenem, meropenem, imipenem/cilastatin[a] • Ceftolozane/tazobactam (*Escherichia coli*)[b]
Pyelonephritis or complicated UTI	• Ertapenem, meropenem, imipenem/cilastatin • Trimethoprim/sulfamethoxazole • Fluoroquinolones[a]	• Ceftazidime/avibactam[b] • Ceftolozane/tazobactam (*E. coli*)[b]
Infection outside urinary tract	• Meropenem, imipenem/cilastatin *Step-down to:* • Fluoroquinolones[a] • Trimethoprim/sulfamethoxazole[a]	• Ceftazidime/avibactam[b] Intra-abdominal infections: • Ceftolozane/tazobactam plus metronidazole (*E. coli*)[b] • Cefepime (if MIC ≤ 1 mg/L)[b] • Piperacillin/tazobactam (if MIC ≤ 2 mg/L)[b]
CRE		
Cystitis	• Fluoroquinolones • Aminoglycosides x1 dose • Trimethoprim/sulfamethoxazole[a] • Nitrofurantoin[a] • Meropenem (ertapenem-resistant, meropenem-susceptible AND CRE testing negative or unavailable)[a]	• Ceftazidime/avibactam • Meropenem/vaborbactam[a] • Imipenem/cilastatin/relebactam[a] • Fosfomycin, oral (*E. coli*)[a] • Cefiderocol[a] • Colistin[a] • Aminoglycosides/plazomicin[a]
Pyelonephritis or complicated UTI	• Fluoroquinolones[a] • Trimethoprim/sulfamethoxazole[a] • Ceftazidime/avibactam[a] • Meropenem/vaborbactam[a] • Imipenem/cilastatin/relebactam[a] • Cefiderocol[a] • Meropenem, extended infusion (ertapenem-resistant, meropenem-susceptible, AND CRE testing negative or unavailable)[a]	• Aminoglycosides/plazomicin[a]
Infection outside urinary tract (ertapenem-resistant, meropenem-susceptible, AND CRE testing negative or unavailable)	• Meropenem, extended infusion[a]	• Ceftazidime/avibactam[a]
Infection outside urinary tract (ertapenem-resistant, meropenem-resistant AND CRE testing negative or unavailable)	• Ceftazidime/avibactam[a] • Meropenem/vaborbactam[a] • Imipenem/cilastatin/relebactam[a]	• Cefiderocol[a] • Ceftazidime/avibactam plus aztreonam [a] Intra-abdominal infections: • Tigecycline, high dose • Eravacycline[a]

(*continued*)

Table 3. Treatment Recommendation for Infections Caused by Extended-Spectrum β-Lactamase and CRE Enterobacteriaceae (*continued*)

Infection Source	Preferred Treatment	Alternative Treatment
Klebsiella pneumoniae carbapenemase or CRE positive	• Ceftazidime/avibactam[a] • Meropenem/vaborbactam[a] • Imipenem/cilastatin/relebactam[a] plus colistin, plus gentamicin, OR plus Fosfomycin, intravenous[b]	• Cefiderocol[a] Intra-abdominal infections: • Tigecycline, high dose • Eravacycline[a]
Metallo-β-lactamase (*NDM*, *VIM*, *IMP*) CRE	• Ceftazidime/avibactam plus aztreonam • Cefiderocol[a] • Fosfomycin, intravenous, plus colistin[b]	Intra-abdominal infections: • Tigecycline, high dose • Eravacycline[a]
Oxacillinase-48 CRE	• Ceftazidime/avibactam[a]	• Cefiderocol[a] Intra-abdominal infections: • Tigecycline, high dose • Eravacycline[a]

[a]Recommended by Infectious Diseases Society of America only.

[b]Recommended by British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party only.

CRE = carbapenem-resistant Enterobacterales.

Information from: Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). Clin Infect Dis 2022a; Hawkey PM, Warren RE, Livermore DM, et al. Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. J Antimicrob Chemother 2018;Supp 3:iii2-78.

with a moderate to high risk of clinically significant inducible AmpC production (Tamma 2022b). One study found no difference in clinical outcomes in patients who received cefepime versus carbapenems for potential AmpC-producing species (Harris 2016). Aminopenicillins, first-generation cephalosporins, and cephamycins are potent AmpC inducers, as well as susceptible to AmpC hydrolysis, whereas piperacillin, ceftriaxone, ceftazidime, and aztreonam are weak inducers but susceptible to AmpC hydrolysis and therefore are not recommended for therapy if AmpC production is suspected (Sanders 1997). The use of piperacillin/tazobactam was compared versus meropenem in patients with ESBL-producing *E. coli* and *K. pneumoniae* bacteremia resulting in higher mortality (12.3% vs. 3.7%) in those who received piperacillin/tazobactam (Harris 2018). A similar trial is currently ongoing to examine the use of piperacillin/tazobactam versus meropenem for AmpC-producing *Enterobacter* spp., *C. freundii*, *Morganella morganii*, *Providencia* spp., or *S. marcescens* bacteremia (Stewart 2021). Ceftriaxone or piperacillin/tazobactam may be considered only in uncomplicated cystitis because of the mild nature of the disease (Tamma 2022b). Of note, for AmpC-producing species that exhibit stable chromosomal de-repression or contain plasmid-mediated *ampC* genes, the AmpC production tends to be constitutive rather than inducible and therefore are non-susceptible to ceftriaxone and ceftazidime by standard testing methods (Tamma 2022b). The use of trimethoprim/sulfamethoxazole, fluoroquinolones, nitrofurantoin or single-dose aminoglycosides for uncomplicated cystitis can be considered for infections caused by Enterobacterales at moderate to high risk of clinically significant inducible AmpC production (Tamma 2022b).

Treatment of CRE includes colistin, tigecycline, and aminoglycosides together with newer agents, including ceftazidime/avibactam, imipenem/cilastatin/relebactam and meropenem/vaborbactam, as well as aztreonam with ceftazidime/avibactam in cases of metallo-β-lactamase-producing strains. Many clinical studies assessing the efficacy of treatment options for CRE were conducted in syndromes that included a high probability of gram-negative pathogens and did not specifically address CRE. Once-daily plazomicin had similar composite cure rates—both clinical (88%) and microbiologic (91.4%)—as meropenem in the treatment

of complicated UTI and acute pyelonephritis caused by Enterobacterales, including MDR strains (Wagenlehner 2019). High-dose tigecycline (200-mg loading dose, followed by 100 mg twice daily) has been used in patients with infections caused by MDR bacteria (De Pascale 2014; Sbrana 2013). Eravacycline has also been examined in the treatment of complicated intraabdominal infections caused by drug-resistant gram-negative bacteria, including ESBL and CRE, for which it was noninferior to meropenem in clinical cure (90.8% vs. 91.2%) (Solomkin 2019). The clinical cure rates for ESBL were 88.9% in the eravacycline group and 81.3% in the meropenem, but only 2 patients had CRE, both in the meropenem group (Solomkin 2019). The REVISIT trial (ClinicalTrials.gov identifier: NCT03329092) is examining the use of aztreonam/avibactam with and without metronidazole versus meropenem with and without colistin for the treatment of resistant gram-negative infections including metallo β-lactamase-producing strains.

PSEUDOMONAS AERUGINOSA

Epidemiology

Pseudomonas aeruginosa is a non-lactose fermenting gram-negative bacilli that is associated with UTIs, bloodstream infections, pneumonias, surgical site infections and burn site infections. A recent CDC estimate of hospital- and community-onset MDR *P. aeruginosa* infections is 32,600 cases, resulting in 2,700 deaths in 2019 (Sievert 2019). Up to 10%–20% of *P. aeruginosa* isolates in the healthcare setting are typically resistant to 1 carbapenem (Sader 2014). *Difficult-to-treat resistance* (DTR) *P. aeruginosa* is defined as non-susceptibility to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, and imipenem/cilastatin or resistance to typical first-line agents that have lower adverse effects (Tamma 2022a; Kadri 2018)

Mechanism of Resistance

Antibiotic resistance for *P. aeruginosa* is typically caused by a combination of different mechanisms, ranging from β-lactamase production, as discussed previously, to increased efflux pump activity or to other cellular membrane changes (Zavascki 2010).

Treatment Options

Treatment for infections caused by *P. aeruginosa* typically relies on the use of cefepime, ceftazidime, imipenem/cilastatin, meropenem, piperacillin/tazobactam, aminoglycosides—and, to some extent, aztreonam and ciprofloxacin—based on the specific antibiotic susceptibility of the strain present and the local susceptibility trends. High-dose extended-infusion therapy with cefepime and piperacillin/tazobactam should be considered in isolates not susceptible to carbapenems but susceptible to traditional β-lactams (Tamma 2022a). Monotherapy with aminoglycosides results in poor clinical outcomes, especially in severe systemic infections, and monotherapy is not recommended outside of urinary source infections or uncomplicated bloodstream infections with source control. Use of colistin may be warranted in patients with carbapenemase-producing isolates for cystitis. For infections caused by DTR *P. aeruginosa*, the source of infection dictates the preferred treatment, as presented in Table 4. Oral fosfomycin is not recommended in the treatment of UTIs caused by DTR *P. aeruginosa* because of the presence of *fosA* gene that results in fosfomycin resistance

Table 4. Treatment Recommendation for Infections Caused by Difficult-to-Treat Resistance *Pseudomonas aeruginosa*

Source of Infection	Preferred Treatment	Alternative Treatment
Cystitis	• Ceftolozane/tazobactam • Ceftazidime/avibactam • Imipenem/cilastatin/relebactam • Cefiderocol • Aminoglycosides x 1 dose	Colistin
Pyelonephritis or complicated UTI	• Ceftolozane/tazobactam • Ceftazidime/avibactam • Imipenem/cilastatin/relebactam, Cefiderocol	Once daily aminoglycosides
Infection outside urinary tract	• Ceftolozane/tazobactam • Ceftazidime/avibactam • Imipenem/cilastatin/relebactam	Cefiderocol

Information from: Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). Clin Infect Dis 2022a.

and the inability for fosfomycin to achieve an adequate concentration for upper UTIs (Ito 2017). Ceftolozane/tazobactam tends to have higher percentage of susceptible clinical isolates, but there is a lack of outcomes data comparing ceftolozane/tazobactam with other newer β-lactam/β-lactamase inhibitors.

Many clinical studies assessing the efficacy of treatment options for DTR *P. aeruginosa* were conducted in syndromes that included a high probability of gram-negative pathogens and did not specifically address DTR *P. aeruginosa*. Ceftazidime/avibactam had similar clinical cure rates (77.4% vs. 78.1%) compared with meropenem for nosocomial pneumonia (81.6% vs. 85.1%) and for complicated intra-abdominal infections when paired with metronidazole (Torres 2018; Mazuski 2016). In addition, ceftazidime/avibactam had similar clinical cure rate compared with best available therapy (91% vs. 91%) for complicated UTIs and complicated intra-abdominal infections caused by *P. aeruginosa* (Carmeli 2016). Ceftolozane/tazobactam had similar mortality rate (24% vs. 25.3%) to meropenem for treatment of nosocomial pneumonia as well as similar clinical cure rates (83% vs. 87.3%) in intra-abdominal infections when paired with metronidazole (Kollef 2019; Solomkin 2015). Imipenem/cilastatin/relebactam had a similar mortality rate (15.9% vs. 21.3%) compared with piperacillin/tazobactam for hospital-acquired or ventilator-associated pneumonia (Titov 2021). Imipenem/cilastatin/relebactam had a similar favorable response (81% vs. 63%) compared with imipenem/cilastatin plus colistin for carbapenem-resistant *P. aeruginosa* infections (Motsch 2020). Cefiderocol was compared with imipenem/cilastatin for MDR gram-negative UTIs and was non-inferior to imipenem/cilastatin (73% vs. 55%; p=0.0004) for the composite outcome of clinical and microbiological cure (Portsmouth 2018). It was also non-inferior to high-dose, extended-infusion meropenem for the treatment of nosocomial pneumonia with respect to all-cause mortality (12.4% vs. 11.6%; p=0.002) (Wunderink 2021). In the treatment of serious infections caused by carbapenem-resistant gram-negative bacteria, cefiderocol had an overall clinical cure rate of 53% versus the best available therapy of 50% at test of cure; however, in the carbapenem-resistant population, the all-cause mortality at day 14 was 25% vs. 11% for the best available therapy (Bassetti 2021). The use of combination antibiotic therapy (aminoglycosides or polymyxin B with a β-lactam) for DTR *P. aeruginosa* infections is not recommended if the in vitro susceptibility has been confirmed (Tamma 2022a). Nebulized antibiotics (i.e., colistin, amikacin, fosfomycin) are also not recommended in the routine treatment of respiratory infections caused by *P. aeruginosa* (Tamma 2022a). Murepavadin is a peptidomimetic antibiotic with a novel mechanism of action and promising in vitro activity versus *P. aeruginosa* by including isolates from the cystic fibrosis population (Diez-Aguilar 2021).

ACINETOBACTER BAUMANNII

Epidemiology

Acinetobacter spp. are aerobic gram-negative coccobacilli that cause opportunistic infections, such as pneumonia, soft-tissue infections, catheter-related infections, and UTIs, in critically ill patients. A recent CDC estimate is 8500 hospitalized cases of carbapenem-resistant *Acinetobacter*, resulting in 700 deaths in 2019 (Sievert 2019).

Mechanism of Resistance

Similar to *P. aeruginosa,* antibiotic resistance for *A. baumannii* is also caused by a combination of different mechanisms. The production of β-lactamases includes carbapenemases such as oxacillinase (OXA)-24/40 and OXA-23 as well as both serine and metallo-β-lactamases. The presence of aminoglycoside modifying enzymes or 16S rRNA methyltransferases eliminate aminoglycosides and plazomicin, whereas upregulation of efflux pumps results in fluoroquinolone resistance.

Treatment Options

Carbapenem-resistant *A. baumannii* poses significant challenges for treatment because it is typically recovered from respiratory or wounds specimens—hence the difficulty in differentiating between true infection and colonization. The presence of carbapenem-resistance typically results in resistance to a broad spectrum of commercially available antibiotics; moreover, a gold standard is lacking for antibiotic regimens used to treat infections caused by carbapenem-resistant *A. baumannii* (Tamma 2022b). Ampicillin/sulbactam is suggested as the preferred agent for mild infections, whereas combination therapy with at least two agents with in vitro activity is recommended for moderate to severe carbapenem-resistant *A. baumannii* infections (Tamma 2022b). Mild infections are UTIs, skin and soft tissue infections, tracheitis, and infections without hemodynamic instability (Tamma 2022b). Alternatives for mild infections are minocycline, tigecycline, polymyxin B (colistin for UTI) or cefiderocol (Tamma 2022b). A recommended regimen for moderate to severe infection ideally includes two agents with in vitro activity, but it could include high-dose ampicillin/sulbactam as one component of the regimen—even for cases in which susceptibility has not been demonstrated—with minocycline, tigecycline, or polymyxin B (Tamma 2022b). Combination therapy of ampicillin/sulbactam with extended-infusion meropenem or cefiderocol has the potential for additive β-lactam toxicity (Tamma 2022b). Data are inadequate to support the use of fosfomycin or rifampin as part of this combination therapy (Tamma 2022b). The use of high-dose extended-infusion meropenem may be considered as part of combination therapy for moderate to severe infection, but not in combination with polymyxin B/colistin without the use of a third agent (Tamma 2022b). The use of cefiderocol can be considered as an alternative treatment regimen in refractory cases or drug

intolerance and as part of a combination regimen (Tamma 2022b). The combination regimen of rifampin with colistin compared with colistin monotherapy for drug-resistant *A. baumannii* pneumonia and blood stream infection susceptible to colistin results in no difference in mortality at 30 days (p=0.95), but a higher microbiological eradication rate results from the combination of colistin plus rifampin (p=0.034) (Durante-Mangoni 2013). Only after demonstration of clinical improvement following an extended-duration regimen should de-escalation to monotherapy be considered (Tamma 2022b). Similar to the treatment of respiratory infection because of *P. aeruginosa*, the use of nebulized antibiotics is not recommended (Tamma 2022b).

STENOTROPHOMONAS MALTOPHILIA

Epidemiology

Stenotrophomonas maltophilia is a non-lactose fermenting gram-negative bacilli that is a rare cause of opportunistic infections in critically ill patients who have received broad-spectrum antibiotics, especially imipenem. The prevalence of *S. maltophilia* is 0.8%–1.68% for isolates of all sources, but it is more commonly isolated in respiratory cultures. followed by bloodstream and then skin and soft tissue infections (Chang 2015). In addition, *S. maltophilia* has been isolated in UTIs, with higher rates for patients in the ICU (up to 3%), and it has also been reported in 9.4% of stool samples (Apisarnthanarak 2003).

Mechanism of Resistance

Stenotrophomonas maltophilia possess two unique chromosomal-mediated Ambler class B metallo-β-lactamases (L1 and L2), 2 RND and SMR-type efflux pumps (*Sme*, *Smr* family*),* and *AME* genes that render aminoglycosides ineffective besides the array of β-lactamases discussed previously (Chang 2015). The development of *SmeDEF* efflux pumps and *Smqnr* genes, which interferes with fluoroquinolone binding to DNA gyrase and topoisomerase, during treatment results in levofloxacin failure (Nys 2019). The *sul* genes carried by integrons can result in high level of trimethoprim/sulfamethoxazole resistance (Apisarnthanarak, 2003).

Treatment Options

Similar to carbapenem-resistant *A. baumannii* infections, infections caused by *S. maltophilia* presents with multiple challenges for the practitioner in terms of the most appropriate treatment regimen. First, *S. maltophilia* is typically recovered from respiratory specimens or as a component of polymicrobial infections, which results in an inherent difficulty in differentiating between true pathogen and colonization. Second, the potential presence of a broad array of β-lactam resistance in *S. maltophilia* infections can result in resistance to a broad spectrum of commercially available antibiotics, including carbapenems. Third, the lack of a gold standard for antibiotic regimens used to treat infections caused by *S. maltophilia* makes selection of the most appropriate regimen difficult. Finally, there is a limited number of reliable Clinical and Laboratory Standards Institute breakpoints available, because trusted breakpoints are limited to just trimethoprim/sulfamethoxazole, cefiderocol, and minocycline. There is concern amongst experts regarding criteria for a MIC breakpoint for ceftazidime and levofloxacin (Tamma 2022b).

For mild infections, trimethoprim/sulfamethoxazole, minocycline, tigecycline, levofloxacin, or cefiderocol monotherapy are considered good options, whereas for moderate to severe infections, the combination of trimethoprim/sulfamethoxazole and minocycline (preferred), combination of trimethoprim/sulfamethoxazole with tigecycline, levofloxacin or cefiderocol, or combination of ceftazidime/avibactam and aztreonam are suggested regimens (Tamma 2022b). Retrospective studies and a meta-analysis have shown no difference in mortality in patients treated with levofloxacin or ciprofloxacin in combination with trimethoprim/sulfamethoxazole; however, potential numeric survival benefit may exist for patients treated with fluoroquinolones over trimethoprim/sulfamethoxazole for all infections (OR 0.62; 95% CI, 0.39–0.99), which was not observed in bacteremia (OR 0.78; 95% CI, 0.48–1.26), even with a decrease susceptibility during treatment (Ko 2019; Wang 2014). In a large retrospective database study including 1581 patients with *S. maltophilia* bacteremia or respiratory tract infections, levofloxacin was associated with a similar mortality risk overall (adjusted OR 0.76; 95 % CI 0.58–1.01) but lower rates of death in patients with lower respiratory tract infection (adjusted OR 0.73; 95% CI, 0.54–0.98) compared with trimethoprim/sulfamethoxazole (Sarzynski 2022).

Cefiderocol has shown very good *in vitro* modeling data, but data are very limited for its use in *S. maltophilia* infections (Kawaguchi 2021). In the treatment of carbapenem-resistant infections, 4 of 5 patients with *S. maltophilia* pneumonia died while treated with cefiderocol versus the best available therapy, which often included polymyxin B; however, 3 of the 5 patients were coinfected with carbapenem-resistant *A. baumannii* (Bassetti 2021).

NOVEL DOSING TECHNIQUES

Antibiotics such as β-lactams—specifically, cefepime, carbapenems, piperacillin and aztreonam—together with vancomycin are characterized as *time-dependent antibiotics*, whereas antibiotics such as aminoglycosides and fluoroquinolones are characterized *as concentration-dependent antibiotic*s. The concentration of β-lactams plays an important role because the efficacy of the antibiotics depends on the time that the concentration of the β-lactams is above the MIC of the pathogen (DeRyke 2006). Because the concentration is determined both by the dose and the volume of distribution, the large amount of fluid resuscitation administered in patients

Patient Care Scenario

A 62-year-old man (weight 92 kg, height 69 inches) is admitted from a long-term care facility to the ICU for acute abdominal pain after a recent colectomy. His temperature is 101°F (38.4°C), blood pressure is 87/55 mm Hg, and heart rate is 122 beats/minute; WBC is 17.2 × 10^3 cells/mm^3. His medical history includes heart failure, hypertension, stroke, chronic kidney disease, and ulcerative colitis; his most recent SCr is 2.5 mg/dL. His home drugs are aspirin 325 mg orally daily, furosemide 20 mg orally twice daily, carvedilol 12.5 mg orally twice daily, and pravastatin 20 mg nightly.

The patient was admitted to the hospital 1 month ago, and acute diverticulitis was diagnosed. During that admission, he underwent total colectomy. After surgery and being stabilized on the hospital floor, he was transferred to a long-term acute care facility to complete 14 days of intravenous ceftriaxone and metronidazole. Although all cultures during the hospitalization were negative, he had elevated WBC values and a fever on postoperative days 3—4.

While at the long-term acute care facility, he completed his intravenous antibiotics and was progressing well until today, when signs of septic shock developed. He is admitted to the ED, where intravenous fluids and norepinephrine are started and 1 dose of piperacillin/tazobactam and vancomycin is administered. Blood cultures were taken prior to the administration of antibiotics. A CT scan reveals a leakage of the end anastomosis of the colectomy, and he is admitted for emergency surgery.

After surgery, the patient is transferred to the surgical ICU and continued on piperacillin/tazobactam and vancomycin. The next day, the blood culture reveals abundant *E. coli*. During rounds, the medical team asked you to review the case and to recommend empiric antibiotics.

ANSWER

The patient's recent exposure to broad-spectrum antibiotics and recent residence at a long-term acute care facility puts this patient at increased risk of MDR bacteria. The selection of empiric antibiotic culture in a patient with septic shock necessitates the consideration of recent antibiotic exposure. Because the preliminary blood culture is currently growing *E. coli* and the recent broad-spectrum antibiotic exposure makes the risk for ESBL highly likely. Because *E. coli* is a known producer of Ambler class A β-lactamases, empiric use of penicillins and cephalosporins would not be appropriate. Although ESBL-producing *E. coli* may be susceptible to cephamycins, β-lactam resistance can develop during therapy as well as other resistance mechanisms, such as the development of efflux pumps. Use of piperacillin/tazobactam may be effective in nonsevere infections because tazobactam may inhibit ESBL activity. However, piperacillin/tazobactam is not ideal because the inoculum effect may develop in a severe infection. The use of carbapenems is the ideal empiric antibiotic treatment for this patient, and most ideal carbapenem for empiric use is meropenem because of the lowest potential risk of neurotoxicity, compared with imipenem/cilastatin, in this patient with history of cerebral vascular accident and with acute renal failure. Considerations can also be made of administering a single dose of aminoglycoside in combination with meropenem to increase the likelihood of appropriate empiric antibiotics. The susceptibility to meropenem must be verified by the microbiology laboratory. The continued use of vancomycin may be appropriate because of the patient's recent surgery and the preliminary status of his blood culture.

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in the ICU plays a large part in the volume of distribution of β-lactams, in addition to the native variability in the specific β-lactams (Goncalves-Pereira 2011). Studies have shown a wide variability in β-lactams achieving its target pharmacokinetic/pharmacodynamic ratio in patients in the ICU (Roberts 2014). This unpredictability has resulted in a low percentage of patients reaching the target pharmacokinetic/pharmacodynamic ratio in dosing of β-lactams, which is further complicated by augmented renal clearance, renal dysfunction, and use of renal replacement therapy, as well as the presence of surgical drains (Roberts 2010).

Because of altered pharmacokinetic parameters in patients in the ICU, use of prolonged or continuous infusion of β-lactam antimicrobials are recommended in patients in the ICU with pathogen having high MIC, patients with septic shock and/or high severity score, patients with lower respiratory tract infections, and patients with infections caused by nonfermenting gram-negative bacilli (Guilhaumou 2019). A Cochrane analysis showed no difference in all-cause mortality (RR 0.89; 95% CI, 0.67–1.20), infection recurrence (RR 1.22; 95% CI, 0.35–4.19), clinical cure (RR 1.00; 95% CI, 0.93–1.08), and superinfection (RR 1.02; 95% CI, 0.94–1.12) in patients

receiving continuous infusion antibiotics (Shiu 2013). A study examining the use of 3-hour prolonged infusion of cefepime, meropenem, and piperacillin/tazobactam in patients in the ICU versus those who received intermittent infusion found no differences in ICU length of stay (10.8 vs. 9.3 days; p=0.138) and hospital length of stay (15.6 vs. 17.0 days; p=0.281) or the time of infection onset to ICU discharge (8.4 vs. 7.8 days; p=0.293) or hospital discharge (12.4 vs. 13.2 days; p=0.481) (Arnold 2013). A small study examining the use of piperacillin/tazobactam, meropenem, and ticarcillin/clavulanate continuous infusion in patients in the ICU with severe sepsis versus those who received intermittent bolus dosing showed more patients who had a plasma antibiotic concentration greater than MIC for all time points (81.8% vs. 28.6; p=0.001) and greater clinical cure (76.7% vs. 50.0%; p=0.032) but no difference in ICU length of stay (7.5 vs. 9.0 days; p=0.50), ICU survival (93.3% vs. 86.7%; p=0.67), or hospital survival (90.0 vs. 80.0; p=0.47) (Dulhunty 2013).

The BLISS study was a small trial that examined continuous infusion of piperacillin/tazobactam, meropenem, and cefepime, compared with a 30-minute intermittent infusion in patients with severe sepsis. A greater clinical cure occurred for patients who received continuous infusion (56% vs. 34%; p=0.011), but this outcome was mostly because of those who received piperacillin/tazobactam (58% vs. 32%; p=0.016) versus those who received meropenem (67% vs. 38%; p=0.064) or cefepime (27% vs. 50%; p=1.0) (Abdul-Aziz 2016). The BLING II study examined the use of piperacillin/tazobactam, meropenem, and ticarcillin/clavulanate continuous infusion in patients with severe sepsis versus those who received intermittent bolus. No difference was found in alive ICU-free days (18 vs. 20 days; p=0.38), clinical cure (52.4% vs. 49.5; p=0.56) and hospital length of stay (16 vs. 14 days; p=0.25), but greater ICU length of stay (7 vs. 6 days; p=0.042) was observed (Dulhunty 2015). A more recent review has shown the potential for improved clinical outcome in critically ill patients who receive piperacillin/tazobactam as a continuous or prolonged infusion (Fawaz 2020)

Use of continuous infusion for time-dependent antibiotics and high dose fluoroquinolones and extended interval aminoglycosides (discussed in more detail in the Therapeutic Drug Monitoring feature) have been promoted to improve bacterial eradication and improve patient outcomes, but their ability to prevent development of antibiotic resistance has been inconclusive. In addition, altered pharmacokinetic parameters, such as larger volumes of distribution, altered protein binding, decreased tissue perfusion, and altered metabolism and clearance presents challenges in achieving adequate dosing of antibiotics in patients in the ICU (Smith 2012). The general recommendation is aggressive dose antibiotic because low doses may fail to achieve adequate levels and hence fail to achieve microbiological eradication and can promote antibiotic resistance. Considerations should also be made regarding the potential for drug toxicities, presence of renal and hepatic failures, the presumed site of infections, and the ability of antibiotics to achieve adequate levels at the site of infection.

Practice Points

Gram-negative antibiotic resistance is a major problem encountered by clinicians within the ICU. Considerations should be made regarding the potential for resistant infections and the appropriate treatment, as follows:

- **Antibiotic resistance is associated with previous hospital stay, presence of chronic invasive devices, prior antibiotics, immunosuppression, and other MDR risk factors.**
- **Using RDT can aid in the rapid identification of antibiotic-resistant genes and allow timely implementation of appropriate antibiotics.**
- **Treatment of resistant gram-negative infections require the use of many newer antibiotics, which include novel β-lactam/β-lactamases inhibitors as well as cefiderocol.**
- **Novel dosing techniques such as continuous/prolong infusion may improve clinical outcomes in patients.**

CONCLUSION

The development of antibiotic resistance in gram-negative pathogens is increasing amid the selection pressure exerted by increasing use of antibiotics. Selection of appropriate antibiotic therapy is an important decision for clinicians, especially with higher resistance rates within patients in the ICU. The choice of empiric antibiotic therapy in severe infections must be a sufficiently broad-spectrum approach to cover the most likely pathogens, while also considering patient- and pathogen-specific risk factors and local susceptibility patterns. Antibiotics must be dosed appropriately for the altered pharmacokinetic and pharmacodynamic properties in the ICU setting, accounting for patients renal or hepatic dysfunction, to meet pharmacodynamic targets. Use of novel diagnostic techniques together with understanding of the potential resistance present in various gram-negative pathogens will allow the selection of the most appropriate antibiotic regimens and improve patient outcomes.

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Self-Assessment Questions

Questions 1-3 pertain to the following case.

A.K., a 74-year-old man, presents to the ED with a 2-day history of fever and altered mental status. He was just recently hospitalized for 1 week with a UTI caused by *Escherichia coli* and treated with cefepime for 14 days before being discharged to a skilled nursing facility. A.K.'s medical history includes diabetes, hypertension, dyslipidemia, and benign prostatic hyperplasia requiring intermittent Foley catheterization leading to frequent UTIs. A.K.'s home drugs include glipizide, lisinopril, aspirin, atorvastatin, tamsulosin, finasteride, and sevelamer. His physical examination is notable for temperature 101.5ºF (38.6ºC), blood pressure 98/42 mm Hg, heart rate 98 beats/minute, and respiratory rate 18 breaths/minute. His laboratory values include BUN 18 mg/dL, Hct 22%, Hgb 7.4 g/dL, potassium 5.4 mEq/L, SCr 2.9 mg/dL, sodium 138 mEq/L, platelet count 54,000 cells/mm^3, and WBC 19.4 × 10^3 cells/mm^3. His peripheral blood cultures are currently growing gram-negative bacilli, lactose fermenting. A.K. is admitted to the medical ICU for sepsis.

1. Which one of the following would most justify the use of rapid diagnostic testing (RDT) for A.K.?

   A. It is gold standard for identifying the specific pathogens causing infections.
   B. It is more accurate in identifying the specific pathogens causing infections.
   C. It can decrease the time from empiric broad-spectrum to targeted antibiotics.
   D. It is relatively inexpensive to set up.

2. Which one of the following is best to recommend in the early treatment of A.K.'s infection?

   A. Kirby–Bauer disk diffusion
   B. Matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF)
   C. AdvanDX peptide nucleic acid fluorescence in situ hybridization
   D. Broth dilution

3. A.K.'s previous urine culture demonstrates the following susceptibility profile:

Escherichia coli

Antibiotic	Interpretation
Ampicillin	R
Ampicillin/sulbactam	R
Cefazolin	R
Ceftriaxone	R
Cefepime	R
Ceftriaxone	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Meropenem	S
Nitrofurantoin	R
Piperacillin/tazobactam	I
Sulfmethoxazole/trimethoprim	R
Tetracycline	R

   Which one of the following is the most likely β-lactam resistance mechanism for A.K.'s UTI?

   A. AmpC
   B. CTX-M
   C. OXA
   D. VIM

4. A 53-year-old man with hypotension is admitted into the ICU from his long-term care facility. His medical history also includes anoxic brain injury following a pulseless electric activity arrest (1 year ago). The patient has a chronic Foley catheter and a history of frequent UTIs treated with sulfamethoxazole/trimethoprim; ciprofloxacin; and, most recently, cefuroxime (completed 2 weeks ago). His vitals on admission included temperature 101ºF (38.5°C), heart rate 111 beats/minute, and blood pressure 85/52 mm Hg; laboratory tests results include WBC 17.1 × 10^3 cells/mm^3. Preliminary microbiological report reveals a urine culture growing 100,000 CFU/mL of *Klebsiella pneumoniae* with susceptibility pending. Which one of the following is best to recommend initiating as empiric antibiotic for this patient?

   A. Ceftriaxone
   B. Levofloxacin
   C. Cefepime
   D. Meropenem

Questions 5–7 pertain to the following case.

A.H., a 24-year-old man, is admitted to the neurosurgery ICU with continued fever and hypotension. The patient was in a motor vehicle crash that resulted in an intracranial bleed requiring a craniotomy and the placement of a ventricular peritoneal shunt. A.H.'s shunt was previously complicated by infection with *Pseudomonas aeruginosa* resulting in treatment with 3 weeks of cefepime. After some initial improvement, his mental status has declined and he is now febrile and hypotensive.

5. Which one of the following is best to recommend initiating as empiric antibiotic for A.H.?

   A. Cefepime
   B. Piperacillin/tazobactam
   C. Meropenem
   D. Ciprofloxacin

6. A.H.'s shunt culture grew *P. aeruginosa* with the following initial susceptibility

Pseudomonas aeruginosa

Antibiotic	Interpretation
Cefepime	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Meropenem	R
Piperacillin/tazobactam	R

   Which one of the following is best to recommend initiating for A.H.?

   A. Imipenem/cilastatin
   B. Ceftazidime/avibactam
   C. Colistin
   D. Tigecycline

7. Which one of the following is the most likely β-lactam resistance mechanism for A.H.'s *P. aeruginosa*?

   A. AmpC
   B. IMI
   C. OXA
   D. TEM

Questions 8–12 pertain to the following case.

C.K., a 64-year-old man who resides in a long-term care facility, was admitted to the medical ICU with dyspnea, fever, and hypotension. The patient has a medical history of cerebrovascular accident with a chronic tracheostomy and percutaneous gastrostomy tube with frequent admissions to the hospital because of pneumonia. C.K.'s tracheal aspirate grew *Acinetobacter baumannii* during his last admission (2 months ago), resulting in treatment with 2 weeks of meropenem together with levofloxacin. After some initial improvement, his respiratory status declined, requiring intubation and started on norepinephrine. Chest radiography shows focal infiltrates in the right lower lobe.

8. Which one of the following would be the most useful in the rapid identification of the potential antibiotic susceptibility of C.K.'s pneumonia?

   A. Tracheal aspirate culture
   B. Sputum culture with Unyvero Panel
   C. Blood culture with MALDI-TOF
   D. Bronchoalveolar lavage culture with FilmArray Panel

9. Which one of the following is best to recommend initiating as empiric antibiotic for C.K.?

   A. Cefiderocol and linezolid
   B. Ampicillin/sulbactam and tigecycline
   C. Meropenem extended infusion and vancomycin
   D. Colistin, rifampin and vancomycin

10. C.K.'s tracheal aspirate culture grows *A. baumannii* with the following initial susceptibility:

Acinetobacter baumannii

Antibiotic	Interpretation
Ampicillin-sulbactam	R
Aztreonam	S
Cefepime	R
Ciprofloxacin	R
Doxycycline	S
Gentamicin	R
Levofloxacin	R
Meropenem	R
Piperacillin/tazobactam	R

   Which one of the following is best to recommend as appropriate antibiotic for C.K.?

   A. Cefiderocol
   B. Ceftazidime/avibactam
   C. Tigecycline and colistin
   D. Ampicillin/sulbactam and minocycline

11. Which one of the following is the most likely β-lactam resistance mechanism for C.K.'s *A. baumannii*?

   A. *ampC*
   B. IMP
   C. TEM
   D. CTX-M

12. It is 1 month after completion of the last antibiotic regiment. C.K. is now intubated and his bronchoalveolar lavage culture grows *Stenotrophomonas maltophilia* with the following initial susceptibility:

Stenotrophomonas maltophilia

Antibiotic	Interpretation
Cefepime	R
Gentamicin	R
Levofloxacin	S
Meropenem	R
Minocycline	R
Piperacillin/tazobactam	R
Trimethoprim-sulfamethoxazole	R

Which one of the following is best to recommend for C.K.?

A. Minocycline monotherapy
B. Ciprofloxacin monotherapy
C. Trimethoprim/sulfamethoxazole with tigecycline
D. Cefiderocol with levofloxacin

Questions 13–15 pertain to the following case.

S.D., a 68-year-old woman, is admitted to the hospital for shortness of breath. Her medical history includes diabetes mellitus, hypertension, and morbid obesity, but she has avoided coming to health care setting for fear of doctors. S.D.'s current drugs include insulin glargine, insulin aspart, lisinopril, and metoprolol. She complains of shortness of breath, fever, chills, and loss of appetite over the past 2 days. She has just finished a 5-day course of moxifloxacin that she obtained at an urgent care center. Examination results are: temperature 101.5°F (38.6°C), heart rate 98 beat/minute, respiratory rate 31 breaths/minute, heart rate 120 beats/minute, and blood pressure 98/42 mm Hg. Chest radiography reveals a dense consolidation in the right lower lobe. S.D. is intubated, started on linezolid, and admitted to the ICU.

13. Besides linezolid, which one of the following is the best empiric antibiotic regimen to recommend for S.D.?

    A. Levofloxacin
    B. Ceftriaxone and doxycycline
    C. Cefepime
    D. Meropenem and azithromycin

14. S.D. initially improved but became hypotensive after 10 days of antibiotic therapy. She was started on norepinephrine and chest radiography continues to reveal a dense consolidation in the right lower lobe that was unchanged. A new respiratory culture is now growing gram-negative bacilli, non-lactose fermenting, while the FilmArray Panel indicates *P. aeruginosa* and *S. maltophilia*. Which one of the following is best to recommend as empiric antibiotic for S.D.?

    A. Meropenem
    B. Ceftazidime/avibactam
    C. Trimethoprim/sulfamethoxazole with cefiderocol
    D. Minocycline with levofloxacin

15. Three months after the previous admission. S.D. returns with urinary frequency with pyuria. Urinalysis indicates a UTI but the patient does not have any signs of flank pain, hemodynamic instability, or other systemic symptoms. S.D.'s urine culture returns with the following susceptibility:

Escherichia coli

Antibiotic	Interpretation
Ampicillin	R
Ampicillin/sulbactam	R
Cefazolin	R
Cefepime	R
Ceftriaxone	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Meropenem	S
Nitrofurantoin	S
Piperacillin/tazobactam	R
Sulfamethoxazole/trimethoprim	R
Tetracycline	S

Which one of the following is best to recommend for S.D.?

A. Nitrofurantoin
B Meropenem
C. Trimethoprim/sulfamethoxazole
D. Ceftazidime/avibactam