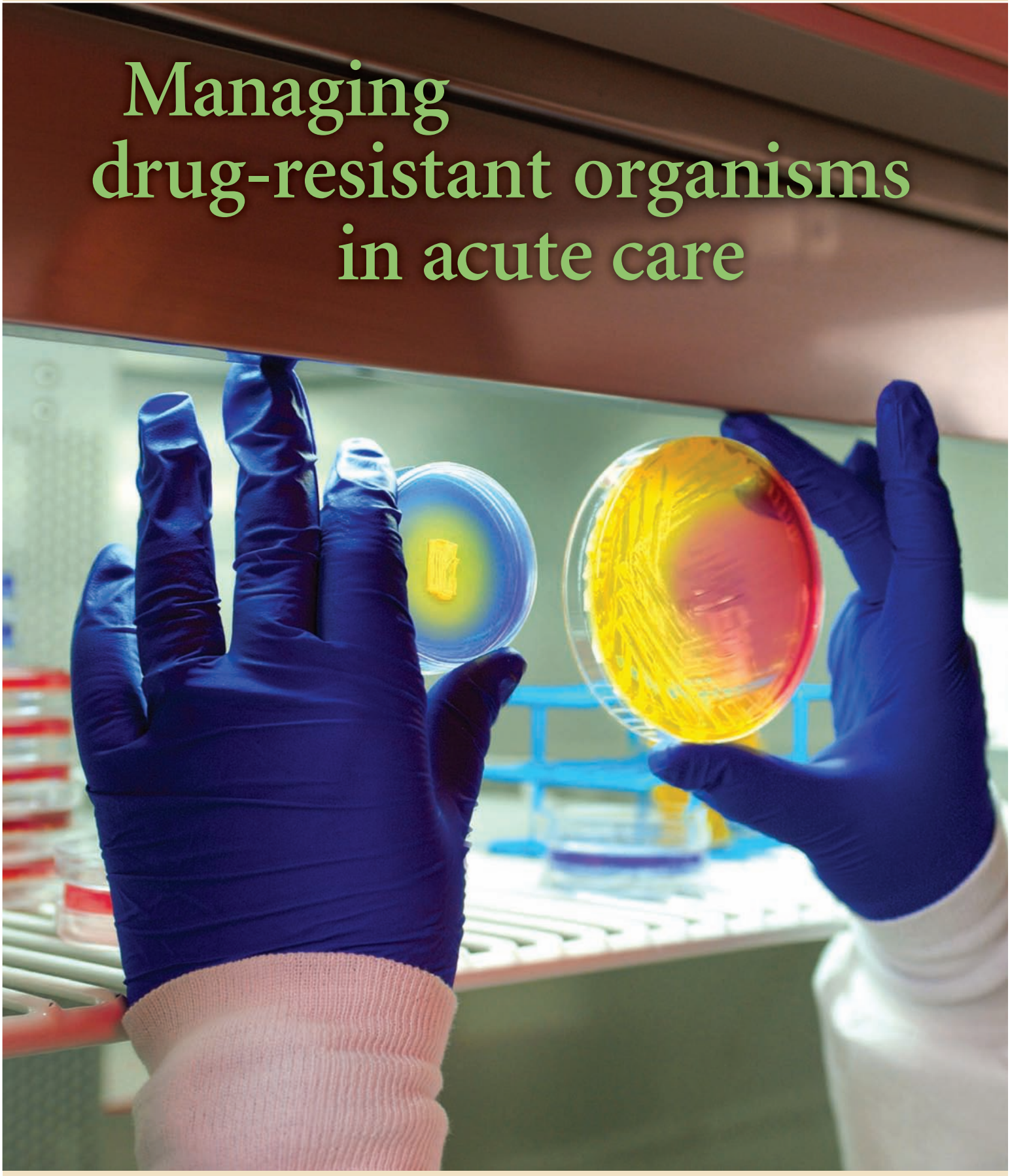
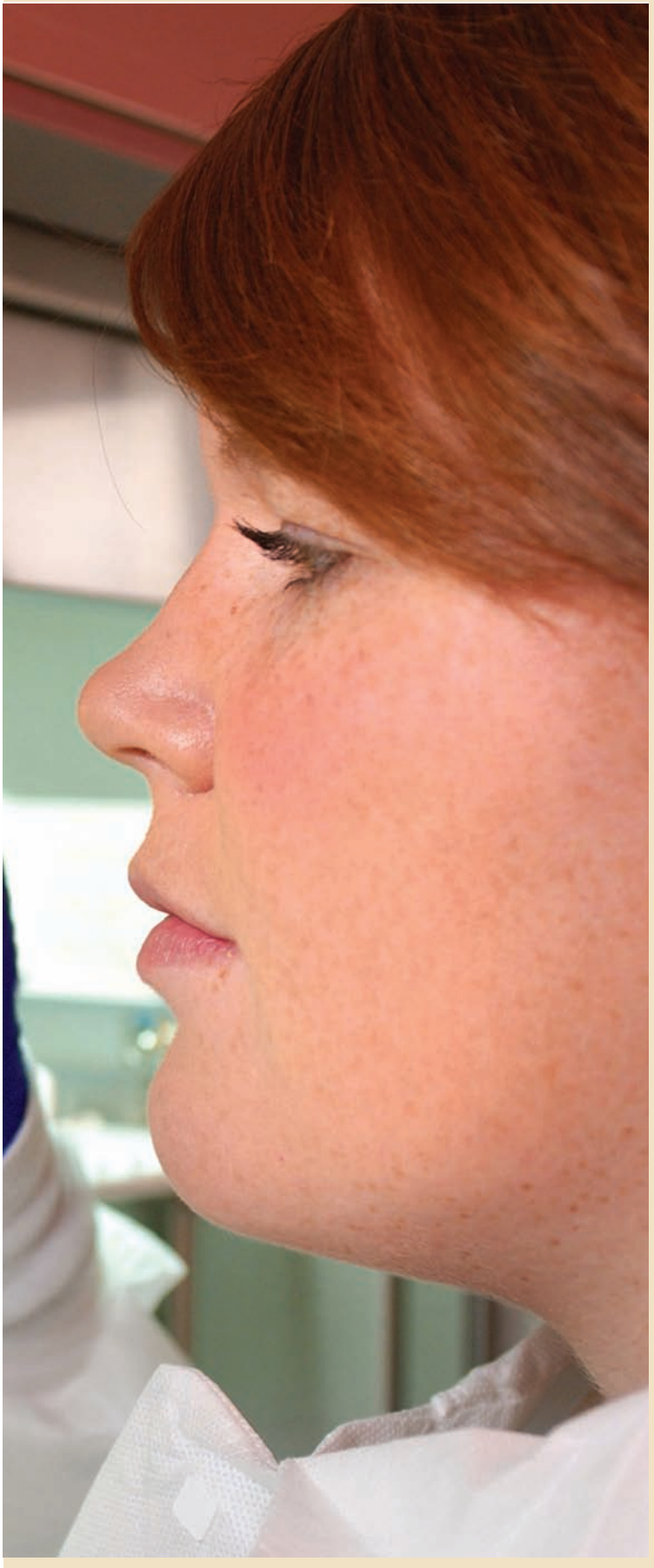
Managing drug-resistant organisms in acute care





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Abstract: The purpose of this article is to provide practitioners with therapeutic considerations for infections caused by drug-resistant organisms in the acute care setting. Proper identification of organisms and appropriate use of antibiotics are imperative strategies to help reduce the development and spread of antimicrobial resistance.

By Kimberly L. Nealy, PharmD, BCPS; Delilah J. McCarty, PharmD, BCACP, CPP, CDE; and J. Andrew Woods, PharmD, BCPS

Antimicrobial resistance is an ever-worsening issue that creates challenges for NPs when caring for patients with infections. A 2013 CDC report estimated that antimicrobial-resistant infection (ARI) incidences exceed 2 million cases in the United States annually.[1] ARI-associated patient mortality is still twice as high compared with other hospitalized patients even when the confounding variables of ICU stay, healthcare-associated infections (HAIs), and the acute physiology and chronic health evaluation (APACHE) score are accounted for.[2] Patients with ARI also tend to have longer hospital stays in addition to higher healthcare-related costs.[1-3]

Immunocompromised patients and those undergoing dialysis or surgery are at higher risk for infectious complications.[1] Patients in these groups often require longer hospitalizations, multiple rounds of antibiotics, and have invasive medical devices most commonly resulting in urinary tract, bloodstream, or lower respiratory tract infections.[4] Antimicrobial resistance further adds to the infection management complications among these patients. Several of the most life-threatening infectious pathogens have known resistance against currently available antimicrobials.

Keywords: antibiotics, antimicrobial-resistant infections, healthcare-associated infections

The CDC has identified the following microbes as serious threats: methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Enterococcus* (VRE); extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*; multidrug-resistant (MDR) *Pseudomonas aeruginosa*; MDR *Acinetobacter*; drug-resistant *Campylobacter*; fluconazole-resistant *Candida*; drug-resistant nontyphoidal *Salmonella*; drug-resistant *Salmonella typhi*; drug-resistant *Shigella*; drug-resistant *Streptococcus pneumoniae*; and drug-resistant tuberculosis.[1] Additionally, the CDC lists carbapenem-resistant *Enterobacteriaceae*, *Clostridium difficile*, and drug-resistant *Neisseria gonorrhoeae* as urgent threats (see *Preferred treatment options for managing drug-resistant organisms*).[1]

Gram-positive infections

Methicillin-resistant *Staphylococcus aureus*. *Staphylococcus aureus* is one of the most common pathogens associated with skin and soft tissue infection (SSTI), bloodstream infection ([BSI] or bacteremia), and healthcare-associated pneumonia.[5] MRSA accounts for more than half of all *S. aureus* isolates.[6] MRSA strains, community-associated (CA-MRSA), and healthcare-associated (HA-MRSA) differ in regards to their clinical and molecular epidemiology.

CA-MRSA most commonly manifests as SSTIs in young, otherwise healthy individuals without recent healthcare exposure.[7] Uncomplicated CA-MRSA SSTIs in immunocompetent patients may be treated with abscess drainage alone.[8] In contrast, patients with signs and symptoms of systemic infection and those with comorbidities should be treated with antibiotics. The vast majority of CA-MRSA strains remain susceptible to trimethoprim-sulfamethoxazole, tetracyclines, and clindamycin.[9,10] By definition, HA-MRSA infections are contracted following hospitalization stay over 48 hours or present within 12 months of hospital discharge as a direct result of hospitalization (for example, MRSA SSTIs associated with a surgical incision).[11]

In addition, several risks for HA-MRSA infection have been elucidated, including: prolonged hospitalization (especially hospitalizations that involve ICU); residence in a long-term care facility; antibiotic use; hemodialysis; colonization with MRSA; and proximity to others with MRSA colonization or infection.[12] HA-MRSA is associated with severe, invasive infections, including bacteremia, pneumonia, and complicated SSTIs (also known as acute bacterial skin and skin structure infections).[11] Vancomycin remains the mainstay of therapy in treating invasive MRSA infections, although the minimum inhibitory concentration (MIC) creep phenomenon (a reported overall decrease in the susceptibility of *S. aureus* isolates to vancomycin in various geographic regions) has raised concern regarding its future efficacy.[8,13]

Vancomycin alternatives should be considered for treating pathogens that are not susceptible to vancomycin (for example, vancomycin intermediate *Staphylococcus aureus* [VISA]) as well as in the setting of vancomycin intolerance or subclinical response to vancomycin. Linezolid is an acceptable alternative to vancomycin in treating MRSA pneumonia and complicated SSTIs.[14,15] Linezolid's role in treating MRSA bacteremia is unclear. Daptomycin is a suitable substitute for vancomycin for treating MRSA bacteremia (including endocarditis and complicated SSTIs) but should never be used for treating MRSA pneumonia.[16-18] Additional alternatives to vancomycin include tigecycline, ceftaroline, telavancin, and quinupristin-dalfopristin.

Vancomycin-resistant *Enterococcus*. Considered normal gastrointestinal tract flora, enterococci are rarely virulent; however, VRE are an increasingly common and concerning cause of HAIs.[5] *Enterococcus faecalis* and *Enterococcus faecium* are the most commonly isolated species of the genus with documented vancomycin-resistance rates of greater than 9% and 80%, respectively.[5] VRE infections are most often associated with patients in the ICU, especially those with intravascular devices and/or urinary drainage catheters. In addition, immunosuppressed patients are particularly vulnerable to VRE infections. Other risk factors include prolonged hospitalization (greater than 72 hours), residence in long-term-care facilities, and prolonged antibiotic exposure.[19,20]

A clinician must first decide whether the isolate represents colonization or infection when addressing a VRE-positive microbiological report. Source control (the removal/replacement of catheters and surgical management of localized infections) should always be the primary intervention in treating a VRE infection. The intrinsic resistance to many antibiotics is the major challenge in pharmacotherapeutic management of a VRE infection. Despite high rates of resistance, increasing incidence, and high mortality, there remains a dearth of clinical efficacy data directing the pharmacotherapeutic management of patients with VRE infections.

Linezolid and quinupristin-dalfopristin are two antibiotics currently FDA approved for treatment of VRE infection.[21,22] Quinupristin-dalfopristin is indicated for *E. faecium* only.[23] Although there are insufficient data to support FDA approval for VRE treatment, daptomycin is likely efficacious against these pathogens.[24-26] However, a recent meta-analysis of available retrospective and observational data indicates that, when compared with linezolid, daptomycin may be associated with worse outcomes when treating patients with VRE bacteremia.[27] Tigecycline and telavancin are other antibiotics (with limited anecdotal evidence) that may be used to treat VRE.[28,29]

Preferred treatment options for managing drug-resistant organisms[4,8,31]

Bacteria	Common presentation	Treatment options
Gram-positive		
Community-associated MRSA	SSTIs	• Trimethoprim-sulfamethoxazole • Tetracyclines • Clindamycin • Linezolid***
Healthcare-associated MRSA	bacteremia, pneumonia, and complicated SSTIs	• Vancomycin*** • Linezolid*** • Daptomycin*,*** • Tigecycline*** • Telavancin*** • Quinupristin-dalfopristin • Clindamycin***
Enterococcus species (VRE)	bacteremia, UTIs, endocarditis, and meningitis	• Linezolid*** • Quinupristin-dalfopristin • Daptomycin*** • Tigecycline • Telavancin***
Gram-negative		
ESBL-producing	hospital-acquired pneumonia, bacteremia, UTIs, and wound infection	• Carbapenems: (imipenem***; meropenem; ertapenem; doripenem) • Tigecycline** • Colistin*** or polymyxin B • Fosfomycin for UTIs
Carbapenemase-producing	hospital-acquired pneumonia, bacteremia, UTIs, and wound infection	• Primary agent in combination regimens • Tigecycline** • Colistin*** or polymyxin B • Adjunct for combination regimens • Carbapenems: (imipenem***; meropenem; ertapenem; doripenem) • Aminoglycoside*** • Rifampin • Fosfomycin for UTIs
MDR *Pseudomonas aeruginosa*	hospital-acquired pneumonia, bacteremia, UTIs, and wound infection	• beta-lactam-beta-lactamase inhibitor combinations: (piperacillin-tazobactam***) • Cephalosporins: (ceftazidime***; cefepime***) • Carbapenems: (doripenem***; meropenem; imipenem***) • Aztreonam*** • Colistin*** • Ciprofloxacin*** • Adjunct for combination regimens • Aminoglycosides*** • Rifampin

MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *Enterococcus*, MDR: multidrug-resistant, ESBL: extended-spectrum beta-lactamase, SSTI: skin and soft tissue infections, UTI: urinary tract infections

*Daptomycin should not be used to treat pneumonia; **Tigecycline should not be used for bacteremia or UTIs; ***Medications are FDA approved for the listed indication

Gram-negative infections

Gram-negative organisms pose a significant healthcare concern, as they are efficient at developing resistance, and their associated infections have a high morbidity and mortality.[30] They may acquire multiple mechanisms of resistance against one antimicrobial agent or employ a single mechanism against several different drugs.[4]

Beta-lactamase production (an enzyme that alters the structure of the antimicrobial molecule) is one of the most troublesome mechanisms of antibiotic resistance identified

among Gram-negative organisms. Several subtypes of beta-lactamases have been identified and classified, including carbapenemases (notably *Klebsiella pneumoniae* carbapenemases), extended-spectrum beta-lactamase, and metallo-beta-lactamases.[30] Carbapenemase enzymes decrease the efficacy of a wide spectrum of antimicrobials, including carbapenems, penicillins, cephalosporins, and potentially aztreonam.[4] Aside from beta-lactamase production, *Pseudomonas aeruginosa* has been associated with several other resistance mechanisms, including enzyme production against aminoglycosides and the use of efflux pumps.[31] Resistance genes are oftentimes encoded on transmissible plasmids, which facilitate resistance spread between organisms. Plasmids carrying beta-lactamase enzymes may also harbor resistance genes against other antimicrobial agents, such as aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole, further limiting treatment options.[31]

Antimicrobials reserved for treating resistant Gram-negative infections

Tigecycline is a parenteral minocycline derivative that is approved for use in complicated SSTI and intra-abdominal infections. The medication can be used against several ESBL- and carbapenemase-producing *Enterobacteriaceae* (including *Klebsiella species*) and *Acinetobacter*; however, it is not effective against *Pseudomonas* or *Proteus*.[4] Additionally, due to low concentrations at the infection site, it should not be used for urinary tract or BSIs. Clinical experience with this agent for resistant Gram-negative infections is limited.[4] It is often used in combination with other agents to treat resistant infections.[30,32,33]

Implementing an antimicrobial stewardship program within healthcare systems improves the prescribing patterns of antibiotics.

Polymyxins, including polymyxin B and colistin, were used for Gram-negative infections in the 1940s but withdrawn from clinical use due to high rates of nephro- and neurotoxicity.[34,35] These agents have recently resurfaced as infections, with MDR Gram-negative organisms becoming more prevalent. Evaluating recent use has revealed that the incidence of these toxicities is less than suspected despite early reports of toxicity. Nephrotoxicity is associated with cumulative doses, combinations with other nephrotoxic medications (including nonsteroidal anti-inflammatory drugs), and hypoalbuminemia; however, this effect seems to be reversible after discontinuation.[34,35] Neurotoxicity is a rare occurrence but may include ataxia, paresthesias, vision disturbances, and neuromuscular blockade.[34] A lack of consistency with dosing units from one manufacturer to another is one factor that complicates colistin use (available parenterally as colistimethate sodium). To avoid erroneous dosing, clinicians should refer to the package insert to implement the manufacturer recommended dose.

Fosfomycin is available only in an oral formulation in the United States, which may limit its use in severe infections in the acute care setting. Its current use is primarily limited to urinary tract infections (UTIs); it could be a viable option for systemic infections if parenteral formulations were more widely available.[31]

ESBL-producing organisms. Carbapenems are considered first-line therapy for ESBL-producing organisms.[31] In a prospective observational study published in 2004, using a carbapenem in patients with ESBL-producing *Klebsiella pneumoniae* bacteremia (specifically imipenem or meropenem) was associated with lower 14-day mortality than other agents used as monotherapy, including ciprofloxacin, cephalosporins, beta-lactam-beta-lactamase inhibitor, or amikacin.[36] Tigecycline use for ESBL infections is complicated by its inadequate concentrations in the urine and blood but can be considered in other types of infections.[31]

Oral fosfomycin or piperacillin-tazobactam (though the latter is not FDA-labeled for the indication) may be considered in UTIs.[31] Additionally, piperacillin-tazobactam may be used for isolates with *in vitro* susceptibility in other types of infections with suspicion for low bacteria inoculum.[31] Cephalosporins, aminoglycosides, trimethoprim-sulfamethoxazole, and fluoroquinolones are not recommended even for isolates with apparent *in vitro* susceptibility due to a high rate of clinical failure and cross resistance.[31]

Carbapenemase-producing organisms. Treating organisms producing carbapenemases poses a significant challenge, as resistance has been documented to all available antimicrobials.[30,31] Combination therapy with two or more agents has shown superior survival over monotherapy in published reports.[30,32,37] Despite these organisms producing carbapenemases, regimens containing a carbapenem combined with one or more other agents (tigecycline, colistin, or an aminoglycoside) are used.[30,32] A few combinations, which have shown some success in published literature, include: tigecycline and colistin, a carbapenem and colistin, tigecycline and gentamicin, and a carbapenem with tigecycline and colistin or an aminoglycoside.[30,32] Rifampin may have some synergistic activity in a combination regimen against carbapenemase-producing organisms for *E. coli* or *Klebsiella pneumoniae* infections.[30,31]

MDR *Pseudomonas aeruginosa*. MDR *Pseudomonas aeruginosa* treatment is associated with controversy. The merits and risks of monotherapy versus combination therapy have been highly evaluated in the literature with ongoing conflicting results.[31] Agents with potential antipseudomonal activity include: beta-lactam-beta-lactamase inhibitors (piperacillin-tazobactam), ceftazidime, cefepime, carbapenems (doripenem, meropenem, or imipenem-cilastatin), aztreonam, aminoglycosides, and ciprofloxacin.[31] The use of two medications with differing mechanisms of action and/or resistance may improve therapeutic success, as resistance to any of these agents may be present; however, additional costs are incurred with this strategy, and risk of adverse reactions is increased.[31] Colistin is typically reserved for highly-resistant strains and last-line therapy.

Additional management strategies

Other strategies to improve therapeutic outcomes have been used aside from proper antimicrobial therapy. It is important to be aware of appropriate dosing for treating MDR Gram-negative pathogens, as high doses are commonly used. Alternative dosing strategies to optimize pharmacokinetic and pharmacodynamic properties of antibiotics may be beneficial. The dosing of beta-lactam agents via extended or continuous infusion rather than intermittent dosing has been implemented to improve the duration of exposure to therapy. This works particularly well for medications, which have time-dependent efficacy (for example, beta-lactam agents). Higher, less frequent dosing may be employed for agents that are primarily concentration-dependent (aminoglycosides).[38] Additionally, alternative routes of administration are being used (most commonly as adjunct therapy) to deliver medication more directly to the site of infection while potentially decreasing risk of systemic adverse reactions. Agents like tobramycin, colistin, and beta-lactams may be aerosolized for inhalation in pneumonia cases.[31]

Moving forward

Antibiotic resistance is an inevitable and natural consequence of antibiotic use; however, there are ways to mitigate the propagation of antibiotic resistance.[1] Due to the high cost of drug development and the hurdles of implementing clinical trials, few antibiotics are currently in development.[4] Therefore, antibiotic stewardship along with infection prevention protocols (including immunizations and appropriate hand hygiene) should be the focus and foundation of treatment.[1] Improper antibiotic prescribing is a significant contributor to antibiotic resistance. Implementing an antimicrobial stewardship program within healthcare systems improves the prescribing patterns of antibiotics by ensuring that selected antibiotics are not only necessary for treatment but also appropriate for targeted microbes.[1,39] The CDC offers guidance and toolkits to help NPs initiate infection control protocols and antimicrobial stewardship programs.[39] Institutions should be familiar with local patterns of resistance and should utilize this information when choosing empiric regimens. Adherence to and regular enforcement of contact precautions and hand hygiene standards is imperative.[30,39] NP

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Kimberly L. Nealy is an assistant professor of Pharmacy Practice at Wingate University School of Pharmacy, Wingate, N.C.

Delilah J. McCarty is an assistant professor of Pharmacy Practice at Wingate University School of Pharmacy, Wingate, N.C.

J. Andrew Woods is an assistant professor of Pharmacy at Wingate University School of Pharmacy, Wingate, N.C.

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