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CLINICAL UPDATE

Antibiotic Considerations in the Treatment of Multidrug-Resistant (MDR) Pathogens: A Case-Based Review

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The recent rise in antimicrobial resistance among health-care associated pathogens is a growing public health concern. According to the National Nosocomial Infections Surveillance System, rates of methicillin-resistant *Staphylococcus aureus* (MRSA) in intensive care units have nearly doubled over the last decade. Of equal importance, gram-negative agents such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum beta lactamase–producing *Enterobacteriaceae* demonstrate increasing resistance to third-generation cephalosporins, fluoroquinolones, and, in some cases, carbapenems. As a consequence, hospitalists may find themselves utilizing new antibiotics in the treatment of bacterial infections. This case-based review will highlight 8 antibiotics that have emerging clinical indications in treating these multidrug-resistant (MDR) pathogens. ***Journal of Hospital Medicine 2009;4:E8–E15.*** *© 2009 Society of Hospital Medicine.*

KEYWORDS: colistin, dalbavancin, daptomycin, doripenem, ertapenem, linezolid, multidrug-resistant, quinupristin-dalfopristin, tigecycline.

Case 1

A 53-year-old woman with a history of hemodialysis-dependent end-stage renal disease presents with left lower extremity pain and redness for the past 3 days. On physical examination, her temperature is 102.3°F. Erythema, induration, and warmth are noted over her left lower leg and foot. Her history is remarkable for a line-related bloodstream infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) 4 weeks ago. The infected line was removed and replaced with a right-sided subclavian catheter. You note that the new line site is clean, not erythematous, and not tender. In the emergency department, the patient receives a dose of vancomycin for presumed MRSA cellulitis. Your patient wants to know if there are alternative agents for her infection so she does not require hospitalization.

Unfortunately, MRSA has become commonplace to the hospital setting. Among intensive care units in 2003, 64.4% of healthcare-associated *Staphylococcus aureus* infections were caused by MRSA, compared with only 35.9% in 1992; a 3.1% increase per year.[1,2] Increased MRSA rates are not without consequence; a recent review suggests that MRSA infections kill nearly 19,000 hospitalized American patients annually.[3] Of note, MRSA infection rates have also increased among previously healthy individuals. These community-associated isolates (CA-MRSA) often manifest as pyogenic skin and soft-tissue infections (SSTIs). In a recent multicenter study, CA-MRSA accounted for 59% of SSTIs among patients presenting to emergency rooms in the United States.[4] In cases of SSTI, oral agents such as clindamycin, doxycycline, and trimethoprim-sulfamethoxazole have proven successful. For invasive MRSA, vancomycin is still considered the standard treatment; however, several alternatives have emerged in recent years. The advantages and disadvantages of linezolid, daptomycin, tigecycline, and dalbavancin in the treatment of MRSA are described below.

Linezolid

Linezolid (Zyvox),® an oxazolidinone approved in 2000, has been touted for its oral bioavailability, twice-daily dosing, gram-positive coverage, and unique mechanism of action. Like several other antimicrobials, linezolid inhibits bacterial protein synthesis. The drug binds to the 50S ribosomal subunit near its site of interaction with the 30S subunit, preventing formation of the 70S initiation complex.[5] This site of action on the 50S subunit is unique to linezolid; as a result, cross-resistance between linezolid and other antimicrobials that act at the 50S subunit (eg, chloramphenicol, macrolides, aminoglycosides, and tetracycline) does not occur.[6]

The oxazolidinones have excellent bacteriostatic activity against all pathogenic gram-positive bacteria. The U.S. Food and Drug Administration (FDA) approved linezolid for the treatment of serious infections due to vancomycin-resistant enterococci (VRE), including bacteremia, complicated skin and soft-tissue infections (cSSTIs) due to *Staphylococcus aureus* (including MRSA), and nosocomial pneumonia due to *Staphylococcus aureus* (including MRSA) or penicillin-susceptible *Streptococcus pneumoniae* (Table 1).

In retrospective analyses of SSTIs due to MRSA, linezolid was as effective as vancomycin, resulting in higher clinical cure rates and shorter hospitalizations.[7] As a result, linezolid has established a role in the treatment of community-acquired MRSA SSTIs. Evidence limited to case reports and

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TABLE 1. FDA-Approved Indications, Limitations, and Side Effects of Newer Antibiotics

Activity	Agent	FDA-Approved Indications	Limitations in Use	Side Effects
Gram-positive	Daptomycin	cSSTIs; MSSA/MRSA bacteremia; MSSA/MRSA endocarditis	Not indicated for pneumonia (inhibited by pulmonary surfactant)	Reversible myopathy may be exacerbated by use with other medications
	Quinupristin-dalfopristin	Vancomycin-resistant *E. faecium*; group A streptococci or MSSA cSSTIs		Myalgias and arthralgias; infusion site reaction;* thrombophlebitis;* liver enzyme elevation; inhibition of cytochrome p450 34a[†]
	Linezolid	Serious infections due to VRE; MSSA/MRSA cSSTIs; MSSA/MRSA nosocomial pneumonia; pneumonia due to penicillin-sensitive *S. pneumoniae*	Not indicated for catheter-related bloodstream infections or catheter site infections	Myelosuppression; serotonin syndrome;[‡] tyramine reaction; peripheral neuropathy; optic neuropathy
	Dalbavancin	Approval pending for cSSTIs	Not indicated for pneumonia bone and joint infection	Unknown[§]
Gram-negative	Colistin	Gram-negative bacteria that have demonstrated sensitivity to the drug	Not indicated for *Proteus* spp, *Providencia* spp, or *Serratia* spp	Acute tubular necrosis; neurotoxicity[‖]; bronchospasm[¶]
Gram-positive and Gram-negative	Ertapenem	Complicated intraabdominal infections[#]; cSSTIs; acute pelvic infections; complicated UTIs; community-acquired pneumonia; prophylaxis of SSI following colorectal surgery in adult patients	Not indicated for *Pseudomonas*, *Acinetobacter*, *S. maltophilia*	Cross-reactivity with penicillin; cross-reactivity with cephalosporins; caution use if history of seizures
	Doripenem	Complicated intraabdominal infections[#] and complicated UTIs, including pyelonephritis		Cross-reactivity with penicillin; cross-reactivity with cephalosporins; caution use if history of seizures
	Tigecycline	cSSTIs (including those due to MRSA) complicated intraabdominal infections[#]		Nausea and vomiting; tooth discoloration in children

Abbreviations: cSSTI, complicated skin and soft-tissue infection; FDA, U.S. Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SSTI, skin and soft-tissue infection; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci; SSI, surgical site infection.

*Administration via central catheter advised to minimize side effects.[69]

[†]The coadministration of quinupristin-dalfopristin with medications that prolong the QTc interval and are also metabolized by the cytochrome P450-34A system should be avoided.[69]

[‡]Concomitant use of a selective serotonin reuptake inhibitor or adrenergic agent is cautioned.

[§]Early phase II and phase III trials suggest that dalbavancin is very well tolerated. The occurrence of nausea, diarrhea, and constipation was not significant when compared to rates of these symptoms among patients receiving linezolid or vancomycin.[20,21] Of concern: the long half-life of the drug may dictate prolong supportive care for patients who develop serious adverse or allergic reactions.

[‖]Colistin-associated neurotoxicity presents in many forms ranging from paresthesias to apnea. Risk factors for developing neurotoxicity include hypoxia and the coadministration of muscle-relaxants, narcotics, sedatives, and corticosteroids.

[¶]While inhaled delivery decreases the nephrotoxicity and neurotoxicity of colistin, this method may provoke bronchospasm.

[#]For example, appendicitis, pancreatitis, cholecystitis, or peritonitis.

case series suggest that linezolid may also have a role in the treatment of bone and joint infections. In these cases, linezolid was often used because treatment with other agents had failed, the administration of other antibiotics was not indicated due to resistance patterns, the patient refused intravenous therapy, or the patient did not tolerate vancomycin. When such conditions exist, linezolid may be a consideration in cases of osteomyelitis or prosthetic joint infection.[8]

Potential side effects of linezolid may limit its use, especially for patients who require prolonged therapy (Table 1). Of note, as a reversible, relatively weak nonselective inhibitor of monoamine oxidase, linezolid may interact with adrenergic and serotonergic agents. Concomitant of a serotonin agent such as a selective serotonin-reuptake inhibitor (SSRI) and linezolid should be approached with caution. Subsequent serotonin syndrome is characterized by autonomic dysfunction (eg, diaphoresis, tachycardia, hypertension) and neuromuscular hyperactivity (eg, muscle rigidity, clonus, hyperreflexia). Though infrequent, cases of reversible myelosuppression have been reported with linezolid use.[9] Patients who will receive this drug for more than 2 weeks should be monitored for myelosuppression with a weekly complete blood count. Isolated reports suggest that the prolonged administration of linezolid (>28 days) may be associated with peripheral neuropathy and optic neuropathy. While prompt discontinuation of the drug often results in resolution of symptoms, peripheral or optic

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nerve injury can be permanent. The mechanism of injury is unclear, though mitochondrial toxicity is suspected.[10]

Daptomycin

Daptomycin (Cubicin®), a cyclic lipopeptide, was discovered in the early 1980s, but skeletal muscle toxicity led to the discontinuation of early clinical trials. When a change from twice-daily to once-daily dosing in 2003 resulted in fewer adverse events, the FDA approved daptomycin to treat complicated skin and skin-structure infections.[11] Daptomycin binds to the cell membrane via a calcium-dependent process, eventually disrupting the cell membrane potential. The bactericidal effect is limited to gram-positive organisms.[12]

Daptomycin is effective against almost all gram-positive organisms including methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, and VRE.[12] As a result, it has FDA approval for the treatment of cSSTIs. While beta-lactams remain the standard of care for MSSA bacteremia, daptomycin has FDA approval for bloodstream infections and right-sided endocarditis due to MSSA or MRSA (Table 1).[13] Daptomycin has poor penetration into alveolar fluid[14] and is inhibited by pulmonary surfactants; as a consequence, it is not indicated for patients with pneumonia.[15]

Of note, daptomycin is mainly excreted via the kidneys and should be dose-adjusted for patients with a creatinine clearance <30 mL/minute. A reversible myopathy may occur with daptomycin, requiring intermittent monitoring of creatinine kinase if prolonged use is anticipated. Caution should be used with the coadministration of medications that can also cause a myopathy, such as statins.

Tigecycline

Tigecycline (Tygacil)® was approved for use by the FDA in 2005. The first in a class of new tetracycline analogs, the glycylcyclines, tigecycline is notable for its activity against several multidrug-resistant (MDR) organisms, including MRSA, VRE, and *Enterobacteriaceae* carrying extended-spectrum beta-lactamases (ESBL). Tigecycline impairs bacterial protein synthesis by binding to the 30S ribosomal subunit. Due to steric hindrance from an *N*-alkyl-glycylamido group at position 9, tigecycline cannot be removed by most bacterial efflux mechanisms.[16]

Tigecycline has been approved for the therapy of cSSTIs, including those due to MSSA and MRSA. In a pooled analysis of 2 international, multicenter, phase III randomized, double-blind trials, tigecycline was not inferior to vancomycin plus aztreonam in the treatment of cSSTIs. Of note, MRSA eradication rates were similar between patients treated with tigecycline and vancomycin plus aztreonam (78.1% and 75.8%, respectively).[17]

Dalbavancin

Dalbavancin (Zeven™), a new, semisynthetic lipoglycopeptide, was approved by the FDA in late 2007; however, it has not been cleared for marketing. Though dalbavancin is derived from teicoplanin, its lipophilic anchor to the bacterial cell membrane makes the drug more potent than its predecessor. Dalbavancin interferes with bacterial cell wall synthesis by binding to the C-terminal D-alanyl-D alanine of the growing peptidoglycan chains.[18] Enhanced pharmacokinetic properties of dalbavancin (half-life 149-250 hours) allow it to be dosed once-weekly, a novel concept in antimicrobial use.[19]

Like other glycopeptides, dalbavancin maintains in vitro activity against most gram-positive aerobic organisms, including MRSA and penicillin-susceptible and penicillin-resistant strains of *Streptococcus pneumoniae*. Notably, when compared to vancomycin in vitro, the agent is more active against *Enterococcus faecium* and *Enterococcus faecalis* isolates. In a recent phase III double-blind trial, dalbavancin was compared to linezolid for the treatment of cSSTIs. Dalbavancin was not inferior to linezolid (clinical success rate 90% vs. 92%). Of note, 51% of study patients with SSTI had infection due to MRSA. Microbiological response to dalbavancin paralleled the clinical success rate; MRSA eradication rates after dalbavancin and linezolid were 91% and 89%, respectively.[20]

Given its once-weekly dosing, dalbavancin may be an attractive agent in the outpatient treatment of gram-positive bacteremia. In a phase II study, dalbavancin administered as a single 1-g dose, followed by a 500-mg dose 1 week later, was comparable to 14 days of vancomycin for the treatment of catheter-related bloodstream infections (CRBSI) due to coagulase-negative staphylococci or *S. aureus* (including MRSA).[21] Phase III studies are underway. At present, there is no evidence to support the use of dalbavancin for the treatment of pneumonia or bone and joint infections.

Despite the administration of vancomycin, the patient continues to experience fever and chills. Blood cultures drawn in the emergency department are now growing *Enterococcus* species. You review the patient's medical record and notice that she was colonized with VRE on a prior admission. You consider the antibiotic options for serious infections due to VRE.

Though rates of VRE have remained fairly stable in recent years,[22] the pathogen continues to present a challenge to hospital epidemiologists. A national survey in 2004 suggested that nearly 30% of enterococci in U.S. intensive care units display vancomycin resistance.[1] Additional U.S. surveillance data reveals that VRE accounts for 10% to 26% of enterococci hospital-wide.[23,24] In 2005, a meta-analysis noted that bloodstream infections due to VRE resulted in higher mortality rates than those due to vancomycin-susceptible enterococci.[25] This discrepancy is most evident among neutropenia patients.[26] Unfortunately, the options for the treatment of serious infections due to VRE are limited. The advantages and disadvantages of linezolid, quinupristin-dalfopristin, tigecycline, and daptomycin in the treatment for VRE are discussed below.

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Linezolid

Currently, linezolid is the only oral drug that is FDA-approved for the treatment of infections due to VRE, including bacteremia. Notably, linezolid therapy resulted in the cure of 77% of 22 cases of vancomycin-resistant enterococcal endocarditis.[27] Current guidelines by the Infectious Disease Society of America (IDSA) support the use of linezolid in cases of endocarditis due to ampicillin-resistant and vancomycin-resistant *Enterococcus faecium*.[28] Unfortunately, recent reports highlight the emergence of linezolid-resistant VRE,[29] suggesting use of this drug should be limited to circumstances in which other alternatives do not exist.

Quinupristin-Dalfopristin

Quinupristin-dalfopristin (Synercid)® was approved by the FDA in 1999. It is used in the treatment of infections caused by gram-positive organisms and is a combination of 2 semisynthetic pristinamycin derivatives. They diffuse into bacteria and bind to different areas on the 50S ribosomal subunit, thereby inhibiting protein synthesis. Individually, quinupristin and dalfopristin are bacteriostatic but together they are bactericidal.[30]

Quinupristin-dalfopristin has activity against *Staphylococcus aureus* (including MRSA), *Streptococcus pneumoniae*, gram-positive anaerobes, and vancomycin-sensitive and resistant *Enterococcus faecium*. It has little activity against *Enterococcus faecalis*.[31] FDA-approved uses of quinupristin-dalfopristin are limited, but include the treatment of serious infections caused by vancomycin-resistant *E. faecium* (VREF).[32] In a study of 396 patients with VREF the clinical success rate of quinupristin-dalfopristin was 73.6%.[33] The drug also has FDA approval for the use in cSSTIs due to group A streptococci or MSSA.[32] The use of this agent is limited due to its toxicity profile. In cases of serious VRE-related infection, quinupristin-dalfopristin is often only utilized if linezolid cannot be tolerated.

Daptomycin

In vitro studies suggest that daptomycin is active against enterococci, including vancomycin-resistant isolates.[34] However, clinical data on the use of this agent in the treatment of infections due to VRE are lacking. FDA approval for the use of daptomycin in cSSTI included the treatment of 45 patients infected with *Enterococcus faecalis*.[13] In addition, several reports have detailed the successful treatment of VRE bloodstream infections with daptomycin,[35,36] including a case series of VRE endocarditis.[37] To determine the role of this agent in the treatment of invasive infections due to VRE, further study is needed.

You decide to discontinue vancomycin and administer linezolid. The patient's vascular catheter is removed; catheter-tip cultures grow >1000 colonies of VRE. Blood cultures the following day are negative and a new catheter is placed. You ask the patient to continue oral linezolid to complete a 2-week course. A review of her medication list reveals that she is not taking SSRIs or monoamine oxidase inhibitors (MAOIs).

While linezolid has retained its FDA indication for VRE bacteremia, empiric use in suspected cases of CRBSI or catheter site infection is not advised. In an open-label trial among seriously ill patients with intravascular catheter-related infections, linezolid use was associated with a higher mortality when compared to vancomycin/oxacillin. Interestingly, mortality among linezolid-treated patients included those with CRBSI due to gram-negative pathogens, due to both gram-negative and gram-positive pathogens, or due to an identifiable pathogen; mortality rates did not differ among patients with gram-positive infections only.[38]

Case 2

A 27-year-old male with a history of T10 paraplegia following a motor vehicle accident presents with abdominal pain, fever, and chills. He notes that he experiences these symptoms when he has a urinary tract infection (UTI), a frequent complication of his chronic indwelling suprapubic catheter. You review his medical record and notice that he has had prior UTIs with multiple gram-negative rods over the past 2 years, including MDR *Pseudomonas* and *Acinetobacter*. When his urine culture grows >100,000 colonies of gram-negative rods, you initiate meropenem and consider the options for treatment of these MDR pathogens.

According to national U.S. surveillance in 2001, 22% of *Pseudomonas aeruginosa* were resistant to imipenem, an increase of 32% from 1997.[39] More alarming is the recent development of MDR *P. aeruginosa*, a pathogen resistant not only to the beta-lactams (including the carbapenems) but to the fluoroquinolones and aminoglycosides as well.[40] MDR *P. aeruginosa* is virulent, and has been associated with higher rates of mortality, longer hospital stays, and greater cost.[41]

Already equipped with intrinsic resistance to the aminopenicillins and first-generation and second-generation cephalosporins, *A. baumannii* has gained recent notoriety with acquired resistance to beta-lactams, aminoglycosides, fluoroquinolones, and tetracyclines. Most notably, carbapenem-resistant *A. baumannii* has emerged due to enzymes capable of hydrolyzing imipenem. Like MDR *P. aeruginosa*, MDR *A. baumannii* infection has led to longer hospital stays[42] and increased patient mortality[43] when compared to infections with more susceptible strains.

Therapeutic options for these MDR gram-negative pathogens remain limited, but the advent of doripenem and the return of colistin may play a role in treatment. The use of these 2 agents and tigecycline in the treatment of MDR *P. aeruginosa* and/or *A. baumannii* are described below.

Doripenem

In October 2007, the FDA approved the use of doripenem (Doribax),™ a much-anticipated carbapenem. In structure,

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doripenem resembles meropenem and does not require a renal dehydropeptidase I inhibitor (eg, cilastatin).[44] Similar to other beta-lactams, doripenem binds to penicillin-binding proteins (PBPs), inhibiting PBP-directed cell wall synthesis.

Like imipenem and meropenem, doripenem has broad-spectrum antimicrobial activity. It demonstrates in vitro activity against most gram-positive pathogens including MSSA and ampicillin-sensitive enterococci. Doripenem also has in vitro activity against most gram-negative pathogens (including ESBL-producing *Enterobacteriaceae*) and most anaerobes, including *Bacteriodes fragilis*. Most notably, when compared to other carbapenems, doripenem has demonstrated better in vitro activity against *Pseudomonas aeruginosa*.[45] However, clinical implications of this in vitro activity are unclear.

When compared to meropenem or levofloxacin for the treatment of complicated UTIs, doripenem is an effective alternative. Clinical response rates among affected patients were 95% to 96% with doripenem, 89% with meropenem, and 90% with levofloxacin.[46,47] Doripenem was not inferior to meropenem in patients with serious lower respiratory tract infections, and comparable to imipenem-cilastin and pipercillin-tazobactam for the treatment of nosocomial or ventilator-associated pneumonia (VAP).[48,49] Finally, for the treatment of complicated intraabdominal infections, doripenem was not inferior to meropenem; both drugs achieved microbiologic cure rates of $>84\%$.[50]

Currently, doripenem is FDA-approved for the treatment of complicated intraabdominal infections (eg, appendicitis, pancreatitis, cholecystitis, peritonitis) and complicated lower UTIs or pyelonephritis (Table 1). Given its expanded spectrum of activity, use of doripenem should be limited to circumstances in which a MDR pathogen is highly suspected or confirmed.

Colistin

Colistin (Coly-Mycin® M) falls within the family of polymyxin antibiotics, which were discovered in 1947. Colistin has been available for almost 50 years for the treatment of infections caused by gram-negative bacteria, including *Pseudomonas* spp. However, early use of colistin was associated with significant nephrotoxicity. Its use decreased markedly with the advent of new antibiotics that had the same antimicrobial spectrum and a better side effect profile. With the emergence of MDR gram-negative bacteria, colistin has returned to limited clinical use.[51] As a polymyxin, colistin is a cell membrane detergent. It disrupts the cell membrane, causing leakage of bacterial cell content and ultimately cell death.[52]

Colistin has bactericidal activity against most gram-negative bacteria including *Acinetobacter* spp, and members of the family *Enterobacteriaceae* (eg, *Klebsiella* spp, *Escherichia coli*, *Enterobacter* spp), including those producing ESBLs.[53] Colistin is not active against several predominant gram-negative pathogens including *Proteus* spp, *Providencia* spp, or *Serratia* spp (Table 1).

In 2007, several studies suggested that colistin monotherapy was effective for patients with VAP due to MDR *P. aeruginosa* or *A. baumannii* isolate.[54,55] A third trial that year suggested that colistin may have a role in the treatment of MDR *P. aeruginosa* among neutropenic patients. In that study, infected patients receiving colistin monotherapy experienced higher rates of clinical and microbiologic response than those receiving other antipseudomonal agents (eg, beta-lactams or fluoroquinolones if active against the isolate).[56] While uncontrolled studies suggest that the use of colistin in combination with other antimicrobials (including carbapenems, ampicillin-sulbactam, aminoglycosides, and rifampin) may have some success in the treatment of VAP due to MDR *A. baumannii*,[57,58] further trials are needed.

Currently, colistin has FDA approval only for the treatment of acute infections due to gram-negative bacteria that have demonstrated susceptibility to the drug and is therefore administered on a case by case basis. Although it has been used via the inhalation route to treat infections in cystic fibrosis patients, colistin does not have FDA approval for this indication.

Tigecycline

Tigecycline is approved for the treatment of complicated intraabdominal infections based on the results of 2 international, multicenter, phase III, randomized, double-blind trials. In this pooled analysis, tigecycline was as effective and as safe as imipenem/cilastatin. Notably, study patients were not severely ill (baseline APACHE II score of 6.0).[59] FDA approval suggests tigecycline use be focused on intraabdominal infections due to members of the family *Enterobacteriaceae* (eg, *Klebsiella* spp, *Escherichia coli*, *Enterobacter* spp), including those producing ESBLs, vancomycin-sensitive enterococci, and/or MSSA. Notably, tigecycline lacks significant in vitro activity against *Pseudomonas* spp, *Proteus* spp, or *Providencia* spp. It has demonstrated in vitro activity against MDR strains of *Acinetobacter* spp (Table 1).

Given its bacteriostatic activity, tigecycline's effectiveness in the treatment bacteremia is unclear.

In addition, as no published studies have addressed its activity among seriously ill patients, tigecycline is considered a second-line or third-line agent for SSTI and complicated intraabdominal infections. Evidence for use of tigecycline for the treatment of UTIs is lacking and, as a rule, its use should be limited to scenarios in which alternatives for the proven or suspected pathogens do not exist.

The urine isolate is identified as *Escherichia coli*. You review the susceptibility profile and determine that this isolate is an ESBL-producing strain. In addition, the patient's isolate demonstrates resistance to the fluoroquinolones and trimethoprim-sulfamethoxazole. You consider other options for treatment of this ESBL-producing *E. coli*.

According to national surveillance data, more than 20% of *Klebsiella* isolates in U.S. intensive care units produced

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ESBLs in 2003, a 47% increase when compared to 1998.[39] Bloodstream infections due to ESBL-producing isolates have led to increased length of hospital stay,[60,61] increased hospital costs,[4] improper antibiotic use,[5] and, most notably, increased mortality.[61-63] Of concern, ESBLs have been demonstrated within community *Enterobacteriaceae* isolates, most notably due to CTX-M beta-lactamase production among *E. coli*. In addition to ESBL production, these community *E. coli* isolates tend to express fluoroquinolone and trimethoprim-sulfamethoxazole resistance.[64] Carbapenems remain the mainstay of therapy for serious infections due to ESBL-producing organisms. The once-daily dosing of ertapenem makes this agent an attractive alternative for outpatient management.

Ertapenem

Ertapenem (Invanz®) obtained FDA approval for use in the United States in 2001 and in the European Union in 2002.[65] Similar to doripenem, ertapenem blocks cell wall synthesis by binding to specific penicillin-binding proteins (PBPs).

Ertapenem has activity against numerous gram-positive and gram-negative bacteria as well as some anaerobic microorganisms. The FDA-approved indications include complicated intraabdominal infections, cSSTIs, acute pelvic infections, complicated UTIs, and community-acquired pneumonias (Table 1).[66] Of note, in contrast to other carabapenems, ertapenem does not have activity against *Pseudomonas aeruginosa* or *Acinetobacter* spp.[67]

Ertapenem is approved as a single daily dose of 1 g and can be administered intravenously or intramuscularly. Changes in dosing must also be considered for critically ill patients. When administered to patients with VAP, ertapenem achieved a lower maximum concentration and area under the curve.[68] In such patients, it is recommended that the dosage interval be decreased or that a continuous infusion of ertapenem be administered.

The patient's symptoms improve on meropenem. A peripherally-inserted central catheter is placed for the administration of intravenous antibiotics at home. You prescribe ertapenem (1 g/day) for the remainder of a 14-day course.

Conclusions

MDR bacteria continue to present a clinical challenge to hospitalists. Proper treatment of patients infected with these organisms is necessary, as inappropriate antibiotic use for MDR bacterial infections has been associated with longer hospital stays, greater cost, and, in some cases, increased mortality. Unfortunately, antibiotic production and development has declined steadily in the past 25 years. To minimize the rate of antimicrobial resistance, physicians must take care to prescribe antibiotics appropriately. While these promising new agents for resistant gram-positive and gram-negative infections may aid in battling MDR infections, these antibiotics must be used judiciously to maintain their clinical utility. Hospitalists will continue to play an important role in ensuring that hospitalized patients receive the most effective antimicrobial therapy to both treat the infection and prevent the development of resistance.

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