Multidrug-Resistant Gram-Negative Bacteria: Trends, Risk Factors, and Treatments

A worldwide public health problem, antibiotic resistance leads to treatment-resistant infections associated with prolonged hospitalizations, increased cost, and greater risk for morbidity.

Lee S. Engel MD, PhD

CASE

An 80-year-old female nursing home resident with a history of dementia, anemia, atrial fibrillation, hypertension, incontinence, and recurrent urinary tract infections (UTIs), as well as a long-term Foley catheter, is admitted because she was found to be febrile and less responsive than normal. The patient has no drug allergies. Upon admission, she has a temperature of 38.9ºC, heart rate of 92 beats/min, and blood pressure of 106/64 mm Hg. The patient opens her eyes to stimuli but does not speak. Aside from poor dentition and an irregular heart rate, findings on physical examination, which includes a pulmonary and abdominal examination, are normal. Serum chemistries demonstrate a white blood cell (WBC) count of 11,300 cells/mm^3. Her blood urea nitrogen level is 86 mg/dL, and her creatinine concentration is 2.1 mg/dL (calculated glomerular filtration rate of 24 mL/min/1.73m^2). Urinalysis demonstrates 40 to 50 WBCs per high-powered field (hpf), 20 epithelial cells per hpf, 3+ protein, positive nitrites, and leukocyte esterase. Blood and urine samples are sent to the microbiology laboratory for routine culture. The patient is started on IV fluids for hydration and renally dosed empiric antibiotic coverage with piperacillin-tazobactam for a probable UTI and possible sepsis.

Dr. Engel is an assistant professor of clinical medicine and infectious disease and associate program director of the internal medicine residency program in the department of internal medicine at Louisiana State University Health Sciences Center in New Orleans.

INTRODUCTION

Antibiotics have saved the lives of millions of people and have contributed to the major gains in life expectancy over the last century. In US hospitals, 190 million doses of antibiotics are administered each day.[1] Furthermore, more than 133 million courses of antibiotics are prescribed each year for outpatients. However, antibiotic use has also resulted in a major health care challenge—the development and spread of resistant bacteria. Worldwide, antimicrobial resistance is most evident in diarrheal diseases, respiratory tract infections, meningitis, sexually transmitted infections, and hospital and health care–acquired infections.[2] Vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, multidrug-resistant (MDR) *Mycobacterium tuberculosis*,[2] and MDR gram-negative bacteria (Table 1)[3-9] are examples of this emerging crisis.[10] The development of extended-spectrum β-lactamases (ESBLs) and carbapenemases that target gram-negative bacteria has resulted in infections that can be extremely difficult to treat, leading to increased morbidity and mortality.[11]

Most studies define *multidrug resistance* as resistance to more than two classes of antibiotics.[4,11-13] The incidence of infection with MDR gram-negative bacteria is on the rise. Analysis of data from the National Nosocomial Infections Surveillance System from 1986 to 2003 demonstrated a significant increase in antibiotic resistance in gram-negative bacteria isolated from infections in the ICU.[14,15] During this period, there was a tenfold increase in resistance among *Klebsiella* spp, twofold increase in resistance

among *Escherichia coli*, threefold increase in multidrug resistance among *Pseudomonas aeruginosa*, and 20% increase in carbapenem-resistant *Acinetobacter* spp.[4,14] The Study for Monitoring Antimicrobial Resistance Trends (SMART), which began in 2002, is the only worldwide surveillance program designed to monitor longitudinally the in vitro antimicrobial susceptibility of gram-negative bacilli isolated from intra-abdominal infections.[16] SMART demonstrated increased detection of ESBL-producing bacteria from 2003 to 2004. In 2004, the percentages of ESBL-producing *E coli*, *Klebsiella* spp, and *Enterobacter* spp were 10%, 17%, and 22%, respectively.[16]

FACTORS ASSOCIATED WITH ANTIBIOTIC RESISTANCE

Global population demographic changes, human behavior, environmental changes, improved medical technology, bacterial evolution, and the breakdown of public health systems have been associated with the development and spread of antibiotic resistance.[17] With regard to the global population, urban migration, immigration, and increased travel have all increased the spread of antimicrobial resistance. Liberation of sexual practices, institutional child care, and alcohol and drug abuse are behavioral factors that can result in the emergence and spread of resistance. Improved medical technology has resulted in a greater proportion of people living with chronic medical conditions, such as end-stage renal disease and diabetes, that are associated with an increased number and chronicity of infections. Decreased funding for public health initiatives has resulted in decreased ability to prevent disease and to respond to new infectious threats associated with immigration, travel, and natural disasters.

Antibiotic use is the main driving force for the development and selection of drug-resistant bacteria.[2] Self-medication with antibiotics, patient perception, patient compliance, physician prescribing practices, and antibiotic use in hospitals are all associated with the emergence and spread of antimicrobial resistance.[2] While overuse and misuse of antibiotics by doctors and patients have caused most of the rise in antimicrobial resistance, antibiotics used in the farming of food animals has also had significant effect.[18] Globally, half of all antibiotics produced are used in food animals. As a result of antibiotic use, foodborne pathogens, such as *Salmonella* and *Campylobacter*, have developed fluoroquinolone resistance.[18]

Antibiotics select for bacteria with either inherent resistance or resistance acquired through gene mutation or transfer of genetic material.[19] The spread of resistance, mediated through transferable genetic elements such as plasmids and transposons, is associated with epidemics of drug-resistant bacteria.[19] Resistance mechanisms include drug efflux systems, antibiotic-modifying enzymes, outer-membrane protein changes, and antibiotic-target modification.[19,20] Resistance to β-lactam antibiotics often involves production of β-lactamases but can also result from drug efflux pumps or outer-membrane changes that decrease drug permeability.[20] Resistance to aminoglycosides often involves modifying enzymes, efflux systems, and ribosomal RNA methylation.[20] Resistance to fluoroquinolones occurs through target modification of the DNA gyrase, efflux systems, and outer membrane changes.[20]

RISK FACTORS FOR MDR GRAM-NEGATIVE BACTERIAL INFECTION

The frequency of antibiotic-resistant health care–associated infections has increased every year for the last 2 decades. Risk factors for colonization and infection with an MDR gram-negative bacterium include age greater than 65 years, antibiotic exposure within the preceding 90 days, hospital admission for at least 2 days in the preceding 90 days, residence in a nursing home, having an indwelling catheter (central venous, arterial, or urinary), mechanical ventilation, tube feeding, hepatic failure, and long-term hemodialysis.[21-23]

The population in the United States is aging. In 1990, 4% of the population was older than 65 years, and by 2040, this group is projected to account for about 25% of the population.[17] Compared with younger people, older patients are more likely to have comorbid conditions, indwelling medical devices, poor nutritional status, poor functional status, and decreased barrier to infection (such as skin breakdown or diminished cough reflex); these are all risk factors for acquisition of resistant organisms.[24] The incidence of bloodstream infections, pneumonia, and UTIs increases with age.[24] Gram-negative bacteria are associated with 70% of bloodstream

>>FAST TRACK<<

Antibiotic use is the main driving force for the development and selection of drug-resistant bacteria.

TABLE 1. Common Multidrug-Resistant Gram-Negative Bacteria

Bacteria	Common Infections	Common Resistance Mechanisms	Antibiotics for Multidrug-Resistant Strains
Klebsiella pneumoniae	Pneumonia Urinary tract infections Wound infections Bloodstream infections Peritonitis Meningitis	β-Lactamases (extended-spectrum β-lactamases) Carbapenemases Antibiotic-target modification	Carbapenems Amikacin Tigecycline Colistin
Escherichia coli	Urinary tract infections Bloodstream infections Pneumonia Wound infections Peritonitis Cholangitis Meningitis	β-Lactamases (extended-spectrum β-lactamases) Carbapenemases Antibiotic-target modification	Carbapenems Amikacin Tigecycline Colistin
Enterobacter spp	Pneumonia Urinary tract infections Bloodstream infections Wound infections	β-Lactamases (extended-spectrum β-lactamases) Carbapenemases Antibiotic-target modification	Carbapenems Amikacin Tigecycline Colistin
Serratia marcescens	Urinary tract infections Wound infections Pneumonia Bloodstream infections	β-Lactamases (extended-spectrum β-lactamases) Antibiotic-target modification	Carbapenems Amikacin Tigecycline
Acinetobacter baumannii	Pneumonia (ventilator associated) Bloodstream infections Wound infections Urinary tract infections	Multidrug efflux pump Antibiotic-modifying enzymes Antibiotic-target modification	Amikacin Tigecycline Colistin

TABLE 1. Common Multidrug-Resistant Gram-Negative Bacteria *continued*

Bacteria	Common Infections	Common Resistance Mechanisms	Antibiotics for Multidrug Resistant Strains
Pseudomonas aeruginosa	Pneumonia Bloodstream infections Urinary tract infections Wound infections Burn infections Osteomyelitis Meningitis Ocular infections	Intrinsic antibiotic resistance β-lactamases (extended-spectrum β-lactamase) Carbapenemases Multidrug efflux pump Antibiotic-modifying enzymes Reduced outer-membrane permeability	Tigecycline Colistin Amikacin
Stenotrophomonas maltophilia	Pneumonia (ventilator associated) Bloodstream infections Wound infections	Reduced outer-membrane permeability Multidrug efflux pump Antibiotic-modifying enzymes	Co-trimoxazole Tigecycline Colistin
Neisseria gonorrhoeae	Urethritis/cervicitis Pelvic inflammatory disease Disseminated gonorrhea	β-Lactamases Target-site mutation (DNA gyrase/ topoisomerase) Reduced outer-membrane permeability	Cefixime Ceftriaxone Spectinomycin Azithromycin

Data extracted from Volles and Branan[3]; Shorr[4]; Cunha[5]; Michalopoulos and Falagas[6]; Vergidis and Falagas[7]; Chemaly et al[8]; and Jamal et al.[9]

infections in the elderly. While *E coli* remains the most common cause of UTI in the elderly, other pathogens, including *Klebsiella* and *Pseudomonas*, are more common in this group than in younger patients and also have the potential for multidrug resistance.[13] Furthermore, elderly patients are more likely than younger patients to have a complicated UTI due to comorbid disease and the presence of indwelling catheters.[13,24]

Retrospective review has suggested that multidrug resistance occurs in 37% of isolates from UTIs in the ED.[13] *E coli* was the most common MDR gram-negative bacteria isolated.[8] Risk factors for community-acquired UTIs caused by ESBL-producing *E coli* include having more than three UTIs in the preceding year, use of a β-lactam antibiotic in the preceding 3 months, prostatic disease, age greater than 65 years, use of a urinary catheter, the presence of a urologic or neurologic abnormality, and residence in a long-term care facility.[25]

A prospective study designed to develop a predicative model of antimicrobial-resistant gram-negative

bacteremia in the ED revealed that hospitalization in the prior month, prior infection with resistant bacteria, post-transplantation immunosuppressant use, leukopenia (absolute neutrophil count <1,000 cells/mm^3), leukocytosis (white blood cell count >15,000 cells/mm^3), residence in a nursing home, history of stroke, and poor oxygen saturation (SpO_2 <95%) predicted the isolation of resistant bacteria from infected patients.[22] Patients with more than two of the above factors had a predicted resistance rate of approximately 40%, with a sensitivity of 67% and specificity of 75%.[22] Specificity of this model increased when patients had more than four of these risk factors.

IMPACT OF GRAM-NEGATIVE BACTERIAL RESISTANCE

Most studies have demonstrated that MDR gram-negative infections convey increased mortality, longer hospital stays, and higher hospital costs when compared with infections associated with susceptible strains.[4,11,12,26] The mortality rate was 15% greater, length of stay in the ICU was 6 days longer, and an initial inappropriate antibiotic selection was 20% more common for patients with MDR gram-negative blood stream infections than for patients with antibiotic-sensitive gram-negative bacteria.[12] The median hospital cost is about $10,000 to $50,000 greater for infections caused by MDR gram-negative bacteria;[4,10,26] this increased cost is related to longer duration of hospital stays and higher cost of antibiotics used to treat these infections. Furthermore, there is a substantial cost for controlling infections. For instance, the cost of new antimicrobial development is estimated at $1 billion per drug. There is also a large cost associated with enforcing isolation procedures used to reduce the spread of resistant pathogens.[4]

>>FAST TRACK<<

***Pseudomonas* is the second most frequent pathogen isolated from health care–associated pneumonia and skin and soft-tissue infections.**

GRAM-NEGATIVE PATHOGENS OF CONCERN

ESBL-Producing Enterobacteriaceae

Enterobacteriaceae are the family of gram-negative bacteria that includes *Klebsiella* spp, *E coli*, *Enterobacter* spp, *Salmonella* spp, and *Serratia* spp. Among this family, β-lactamase production is the most common mechanism of resistance.[4] The ESBLs produced by Enterobacteriaceae have variable resistance to cephalosporins, penicillins, β-lactamase inhibitors, and monobactams. ESBLs have plasmid-encoded genes associated with a great ability to spread between bacteria.[11] The ESBL-producing phenotype is present in approximately 10% to 15% of the Enterobacteriaceae.[10] ESBL-producing Enterobacteriaceae have traditionally been treated with carbapenems; however, some ESBL-producing Enterobacteriaceae now also produce carbapenemases.[23]

Acinetobacter spp

The *Acinetobacter calcoaceticus-baumannii* complex has emerged as a MDR nosocomial and community-acquired pathogen. *Acinetobacter* was a common wound isolate during Operation Desert Storm and after natural disasters such as the 2004 Asian tsunami.[10] The incidence of *Acinetobacter* has increased in ventilator-associated pneumonia, bloodstream infections, surgical site infections, and UTIs.[10,27] Furthermore, strains of *Acinetobacter* that are resistant to all aminoglycosides, cephalosporins, β-lactams, and fluoroquinolones are increasing in prevalence.[10] These MDR strains are problematic to treat and are associated with more frequent relapses. Antibiotics such as colistin and tigecycline are being employed more frequently in the treatment of MDR *Acinetobacter*.[27]

Pseudomonas aeruginosa

Pseudomonas aeruginosa is associated with a variety of infections, including pneumonia, UTIs, wound infections, and bacteremia. *Pseudomonas* is the second most frequent pathogen isolated from health care–associated pneumonia and skin and soft-tissue infections.[10] *Pseudomonas*, which has intrinsic antibiotic resistance, has also acquired other mechanisms of resistance, including β-lactamases, carbapenemases, and multidrug efflux pumps. Rates of resistance to third-generation/antipseudomonal cephalosporins, carbapenems, and quinolones have continued to rise during the last 10 years.[10] About 30% of MDR *P aeruginosa* exhibited resistance to four antibiotic drug classes (ie, cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones).[27] Agents such as colistin are now being used to treat these MDR strains.[27]

Stenotrophomonas maltophilia

An environmental organism, *Stenotrophomonas maltophilia* is found in almost all types of aquatic

or humid environments, including drinking water.[27] This bacterium is not inherently virulent, but it can colonize the surfaces of medical devices and respiratory tract epithelium. It has been an increasing cause of pneumonia and bloodstream infections in immunocompromised patients. Specific risk factors for infection with *S maltophilia* include an extended stay in a critical care unit, prolonged mechanical ventilation, tracheotomy, exposure to broad-spectrum antibiotics, chemotherapy-induced neutropenia, and leukemia.[28] *S maltophilia* has a high-level intrinsic resistance to many antibiotics, including β-lactams, quinolones, aminoglycosides, and tetracycline, as well as to some disinfectants and silver used to line catheters. Furthermore, it has increasing resistance to co-trimoxazole, the first-line drug used to treat *S maltophilia* infections. Antibiotics such as colistin and tigecycline are now used more frequently to treat co-trimoxazole–resistant *S maltophilia*.[28]

Neisseria gonorrhoeae

Neisseria gonorrhoeae is the second most common sexually transmitted disease in the United States (after chlamydia).[29] In 2007, the US Centers for Disease Control and Prevention updated the treatment guidelines for gonorrhea due to widespread resistance to fluoroquinolones.[29] Current guidelines recommend the use of ceftriaxone, cefixime, spectinomycin, or a single oral dose of azithromycin 2 g (for penicillin-allergic patients).[29] Treatment failure with oral cephalosporins has now been reported in Japan, and its spread is imminent.[30] Unfortunately, there are few good existing antibiotics or agents in development for the treatment of cephalosporin-resistant isolates.

TREATMENT OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

The emergence of MDR gram-negative organisms presents a significant treatment challenge for practicing physicians (see Table 2 for treatment options).[3] Patients with severe sepsis or septic shock should receive broad-spectrum antibiotics until the causative bacterium has been isolated and its susceptibility has been determined. For patients who are severely ill, combination therapy is warranted. After

TABLE 2. Antibiotics For Multidrug-Resistant Gram-Negative Infections

Antibiotic	Dosage[a]	Most Frequently Reported Adverse Events
Carbapenem		
Meropenem	1 g IV every 8 hours	Headache, nausea, vomiting, diarrhea, rash, seizures (imipenem)
Imipenem	500 mg IV every 6 hours	
Ertapenem	1 g IV or IM every 24 hours	
Doripenem	500 mg IV every 8 hours	
Tigecycline	Start 100 mg IV for first dose, then 50 mg IV every 12 hours	Nausea, vomiting, diarrhea
Amikacin	7.5 mg/kg IV or IM every 12 hours[b]	Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity; nephrotoxicity
Colistin (polymyxin E)	2.5 to 5 mg/kg/day IV divided two to four times per day	Neurotoxicity, nephrotoxicity

IV = intravenous; IM = intramuscular
[a] Renal dosing not listed
[b] Peak and trough levels should be monitored
Data extracted from Volles and Branan.[3]

the susceptibilities are known, antibiotic therapy can be de-escalated to narrower-spectrum antibiotics.

There are a limited number of older antibiotics that have activity against MDR gram-negative bacteria; likewise, there are very few new antibiotics in development for the treatment of infections caused by these bacteria.[20,31] The lack of treatment options is due to the cost associated with developing new antibiotics, the withdrawal of many large pharmaceutical companies from antibacterial research and development, and the difficulty of devising antibiotics with novel mechanisms of action.[31] None of the antibacterial agents in clinical trials possesses sufficiently novel modes of action to circumvent antibiotic-resistance mechanisms of gram-negative bacteria.[31] Out of necessity, there has been a resurgence in the use of older antibiotics (eg, amikacin, colistin).[5,6]

Carbapenems

The carbapenems (ie, meropenem, imipenem, ertapenem, doripenem) are β-lactam antibiotics with the broadest spectrum of activity of all drug classes.[3] They are first-line agents for ESBL-producing Enterobacteriaceae and are approved by the FDA for the treatment of intra-abdominal infection; pneumonia; UTI; meningitis; gynecologic infection; bacterial septicemia; bone, joint, and skin infections; endocarditis; and polymicrobic infections.

There are differences between individual carbapenems. Imipenem is administered with cilastatin, which inhibits breakdown of the drug by enzymes in the proximal renal tubule cells. Imipenem has slightly better activity for gram-positive pathogens, while meropenem is slightly more active against gram-negative bacteria. Imipenem commonly lowers the seizure threshold more than the other carbapenems. Ertapenem can be given once daily but does not cover *Pseudomonas*. Doripenem is the newest carbapenem and is more active against *Pseudomonas* than are the other drugs.[7] Unfortunately, many strains of *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* have general resistance to carbapenems.[3] Furthermore, there are now ESBL-producing *Klebsiella* that can produce carbapenemases.[23]

Tigecycline

Derived from minocycline, tigecycline is a glycylcycline that was licensed for use in the United States

in 2005.[31] Glycylcyclines bind to the ribosome five times more strongly than does tetracycline and can overcome common resistance mechanisms described for tetracycline.[8] Tigecycline has broad coverage that includes methicillin-resistant *S aureus*, ESBL-producing *Klebsiella* and *E coli*, and *Acinetobacter*.[3] Tigecycline is not active against *Pseudomonas*, *Morganella*, or *Providencia*. Tigecycline is FDA approved for complicated skin/skin-structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia, including cases with concomitant bacteremia. Tigecycline is bacteriostatic and comes only in a parenteral form. This agent does not require renal dosing, as the liver metabolizes it. Dosing is 50 mg every 12 hours after a 100-mg initial loading dose. The most common adverse effects are nausea, vomiting, and diarrhea.

Tigecycline has proven to be beneficial in the treatment of serious infections in patients with cancer.[8] Tigecycline has activity against ESBL-producing *E coli* and *Klebsiella* and has been used to control outbreaks of carbapenemase-resistant *A baumannii* in an ICU.[9] Resistance has been described and is thought to be related to broad-spectrum efflux pumps.[7]

Amikacin

Amikacin is the aminoglycoside that has the greatest degree of antipseudomonal activity.[27] Amikacin has only one location susceptible to enzymatic inactivation by acetylating enzymes; thus, it is more resistant to inactivation than are gentamicin and tobramycin, which have six locations for inactivation. Amikacin is FDA approved for the short-term treatment of serious infections due to susceptible strains of gram-negative bacteria, including *Pseudomonas*, *E coli*, species of indole-positive and indole-negative

>>FAST TRACK<<

Tigecycline has proven to be beneficial in the treatment of serious infections in patients with cancer.

Proteus, *Providencia* spp, *Klebsiella-Enterobacter-Serratia* spp, and *Acinetobacter* spp. Treatment indications include bacterial septicemia (including neonatal sepsis); serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis), skin, and soft tissue; intra-abdominal infections (including peritonitis); burn infections; postoperative infections (including postvascular surgery); and complicated and recurrent UTIs. At present, amikacin is used as part of combination therapy for an additive or synergistic effect against MDR strains of *P aeruginosa*, *A baumannii*, and Enterobacteriaceae.

Colistin

First discovered in 1947, colistin (polymyxin E) is a cationic polypeptide that was used clinically until it fell out of favor in the 1970s.[6] Colistin binds phospholipids in the outer membrane of gram-negative bacteria, causing cell wall destabilization and cell death. Colistin is bactericidal against many MDR gram-negative bacteria, including *P aeruginosa*, *A baumannii*, *Klebsiella pneumoniae*, and *E coli*.[3,6] Colistin is not active against *Proteus*, *Providencia*, *Burkholderia*, *Neisseria*, or *Serratia*.[3,5,6] Colistin is FDA approved for the treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli, particularly *P aeruginosa* in association with cystic fibrosis. Dosing can be confusing because there are differences in units between the packaging in the United States (mg) and Europe (international units).[6] Dosing in the United States ranges from 2.5 to 5 mg/kg/day divided two to four times a day in patients with normal renal function.[3] Nephrotoxicity and neurotoxicity have been associated with colistin use in the past; however, recent data indicate that toxicity may be less prominent than previously reported.[5] Resistance occurs through changes in the outer membrane of the bacteria.[3]

>>FAST TRACK<<

Sitafloxacin, currently undergoing trials, is a fluoroquinolone that has improved activity in vitro against several gram-negative pathogens.

Future Treatment Options

Sitafloxacin, currently undergoing trials, is a fluoroquinolone that has improved activity in vitro against several gram-negative pathogens, including *Acinetobacter* and levofloxacin-resistant *Pseudomonas*.[31] Antibacterial peptides designed to disrupt bacterial membranes are in development.[31] Antivirulence agents are also being studied. For example, agents designed to inhibit lipopolysaccharide biosynthesis and efflux pump inhibitors are under investigation.[31] However, despite this research, few novel antibiotics are entering phase 1 studies at this time.[31] For this reason, antibiotic stewardship and good infection control measures are of the utmost importance in the battle against the development and spread of MDR gram-negative bacteria.

CASE RESOLUTION AND DISCUSSION

The patient's blood cultures did not grow, but her urine culture grew greater than 100,000 colony-forming units of a *K pneumoniae* that was resistant to ampicillin/sulbactam, aztreonam, cefepime, ceftriaxone, imipenem, meropenem, and ciprofloxacin. The isolate was sensitive to piperacillin-tazobactam but positive for ESBL. It was also sensitive to tobramycin, gentamicin, amikacin, and tigecycline. Based on the results of sensitivity testing and the presence of renal insufficiency, the patient's antibiotic coverage was changed from piperacillin-tazobactam to tigecycline, starting with an initial dose of 100 mg IV and then 50 mg IV every 12 hours. Following the change of antibiotics, the patient's Foley catheter was replaced, her renal function improved with hydration, her temperature and WBC count normalized, and she returned to her baseline functional capacity. This patient had several risk factors for an MDR gram-negative bacterium, including her age, residence in a nursing home, and long-term Foley catheterization. Even though the isolate appeared to be sensitive to piperacillin-tazobactam, the presence of an ESBL would inactivate this antibiotic. Furthermore, this isolate was most likely producing a carbapenemase, as it was resistant to imipenem and meropenem. The physician chose tigecycline instead of an aminoglycoside because tigecycline does not require renal dosing adjustment, and evidence in the published literature suggests that this antibiotic is effective for UTIs. □

REFERENCES

1. American College of Physicians—American Society of Internal Medicine. Antibiotic resistance. American College of Physicians Web site. http://www.acponline.org/patients_families/diseases_conditions/antiobiotic_resistance. Published 2000. Accessed October 25, 2009.
2. World Health Organization. Antimicrobial resistance. Fact sheet 194. World Health Organization Web site. www.who.int/

mediacentre/factsheets/fs194/en. Revised January 2002. Accessed October 25, 2009.
3. Volles DF, Branan TN. Antibiotics in the intensive care unit: focus on agents for resistant pathogens. *Emerg Med Clin North Am.* 2008;26(3):813-34, x.
4. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med.* 2009;37(4):1463-1469.
5. Cunha BA. New uses for older antibiotics: nitrofurantoin, amikacin, colistin, polymyxin B, doxycycline, and minocycline revisited. *Med Clin North Am.* 2006;90(6):1089-1107.
6. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. *Crit Care Clin.* 2008;24(2):377-91, x.
7. Vergidis PI, Falagas ME. New antibiotic agents for bloodstream infections. *Int J Antimicrob Agents.* 2008;32(suppl 1):S60-S65.
8. Chemaly RF, Hanmod SS, Jiang Y, et al. Tigecycline use in cancer patients with serious infections: a report on 110 cases from a single institution. *Medicine (Baltimore).* 2009;88(4):211-220.
9. Jamal W, Salama M, Dehrab N, et al. Role of tigecycline in the control of a carbapenem-resistant Acinetobacter baumannii outbreak in an intensive care unit. *J Hosp Infect.* 2009;72(3):234-242.
10. Slama TG. Gram-negative antibiotic resistance: there is a price to pay. *Crit Care.* 2008;12(suppl 4):S4.
11. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother.* 2008;52(3):813-821.
12. Sostarich AM, Zolldann D, Haefner H, et al. Impact of multiresistance of gram-negative bacteria in bloodstream infection on mortality rates and length of stay. *Infection.* 2008;36(1):31-35.
13. Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *Am J Emerg Med.* 2000;18(2):143-146.
14. Gaynes R, Edwards JR; National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis.* 2005;41(6):848-854.
15. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control.* 2004;32(8):470-485.
16. Rossi F, Baquero F, Hsueh PR, et al. In vitro susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *J Antimicrob Chemother.* 2006;58(1):205-210.
17. Church DL. Major factors affecting the emergence and re-emergence of infectious diseases. *Clin Lab Med.* 2004; 24(3):559-586, v.
18. World Health Organization. Use of antimicrobials outside human medicine and resultant antimicrobial resistance in humans. http://www.who.int/mediacentre/factsheets/fs268/en. Accessed November 3, 2009.
19. Livermore DM. Bacterial resistance: origins, epidemiology, and impact. *Clin Infect Dis.* 2003;36(suppl 1):S11-S23.
20. Chopra I, Schofield C, Everett M, et al. Treatment of health-care-associated infections caused by Gram-negative bacteria: a consensus statement. *Lancet Infect Dis.* 2008;8(2):133-139.
21. Friedmann R, Raveh D, Zartzer E, et al. Prospective evaluation of colonization with extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae among patients at hospital admission and of subsequent colonization with ESBL-producing enterobacteriaceae among patients during hospitalization. *Infect Control Hosp Epidemiol.* 2009;30(6):534-542.
22. Chiang WC, Chen SY, Chien KL, et al. Predictive model of antimicrobial-resistant gram-negative bacteremia at the ED. *Am J Emerg Med.* 2007;25(6):597-607.
23. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. *Lancet Infect Dis.* 2009;9(4):228-236.
24. Caterino JM. Evaluation and management of geriatric infections in the emergency department. *Emerg Med Clin North Am.* 2008;26(2):319-343, viii.
25. Azap OK, Arslan H, Serefhano lu K, et al. Risk factors for extended-spectrum beta-lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. *Clin Microbiol Infect.* 2009 Aug 18. [Epub ahead of print]
26. Evans HL, Lefrak SN, Lyman J, et al. Cost of Gram-negative resistance. *Crit Care Med.* 2007;35(1):89-95.
27. McGowan JE Jr. Resistance in nonfermenting gram-negative bacteria: multidrug resistance to the maximum. *Am J Med.* 2006;119(6 suppl 1): S29-S36.
28. Looney WJ, Narita M, Mühlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. *Lancet Infect Dis.* 2009;9(5):312-323.
29. US Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep.* 2007;56(14):332-336.
30. Tapsall JW. Neisseria gonorrhoeae and emerging resistance to extended spectrum cephalosporins. *Curr Opin Infect Dis.* 2009;22(1):87-91.
31. O'Neill AJ. New antibacterial agents for treating infections caused by multi-drug resistant Gram-negative bacteria. *Expert Opin Investig Drugs.* 2008;17(3):297-302.