CHAPTER 29

Antibiotic-Resistant Bacteria in Returning Travelers

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International travel often brings us into contact with multidrug-resistant (MDR) organisms (MRDOs), especially bacteria. These germs may or may not colonize or infect the traveler, but when they do, they present challenges to the clinician. This chapter will focus on strategies to prevent, diagnose, and treat MRDO infections in international travelers.

OVERVIEW OF ANTIBIOTIC RESISTANCE

Long before the human era, microbes competed for ecological niches in the environment. Thus, ancient bacteria developed the ability to resist the assault of naturally occurring antibacterial substances, especially those made by fungi and other soil-dwelling organisms. By harnessing these substances (and by developing new antibiotics) for clinical use, we have dramatically accelerated this evolutionary process. The more we expose bacteria to these medications, the sooner we select resistant phenotypes. Nobel Laureate Alexander Fleming warned long ago that this process was inevitable and that medical professionals have an ethical responsibility to use antibiotics in a responsible fashion. Less than a century later, his concerns have proven prophetic. Antibiotic resistance to at least one class of drugs has been documented in almost all bacteria studied, including Gram-positive bacteria (e.g., methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and drug-resistant *Streptococcus pneumoniae*), and Gram-negative bacteria (e.g., extended-spectrum beta-lactamase-producing *Escherichia coli*, MDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Enterobacteriaceae*). Some mechanisms of resistance are specific to a particular species, but in many cases the genetic determinants of resistance lie on mobile elements, such as plasmids and integrons, which can move between species. Thus, in some regions of the world there seem to be ideal conditions for the creation and spread of resistant microbes, in which antibiotic use is uncontrolled and sanitation is insufficient. There is no single, reliable, international surveillance system for detecting and reporting antimicrobial resistance. The World Health Organization oversees a consortium of regional laboratories around the globe, but their funding streams and staffing are often insufficient to generate timely data, especially in sub-Saharan Africa. High-quality data are essential for our understanding of this phenomenon, and they are sorely lacking—this situation needs to change right away. However, the trend is clear: many bacterial infections are becoming tougher to treat worldwide, including in the tropics.

There is no hope of eradicating pathogenic bacteria from the face of the earth with antibiotics—resistance is inevitable. The global question is whether we can reduce, delay, and anticipate the emergence of resistance in a way that helps humans live side-by-side with bacteria in a sustainable way. Our understanding of the human microbiome—the universe of microorganisms on and inside us—is still incomplete. But we do know that more than 90% of the cells on us and in us are microorganisms, so by the numbers we are more "them" than "us." The notion of human dominance over the microscopic world is naïve, and a more nuanced view of our position in the world is called for. For medical providers

dealing with MDRO infections in their individual patients, these questions have very urgent clinical meaning.

PREVENTION OF MDRO INFECTION: PUBLIC HEALTH

Reducing the threat of MDROs on an international scale will require coming to terms with several key factors that are currently out of control.

- *Meager drug pipeline*. New antibiotics may help turn the tide, but the current pace of progress is discouraging. Industry has precious few financial incentives to develop novel agents, because the process is time-consuming and expensive. And with resistance on the rise, there is concern that new agents will have limited effective lives—and, thus, limited profit potential. A new "public-private partnership" model may be called for, in which government incents industrial activity via financial rewards beyond traditional drug sales. Viewing these drugs as national assets, rather than simple profitable commodities, may yield meaningful change.
- *Ineffective infection control*. Limiting the spread of infection between patients is common sense, with an importance easily grasped by physicians. However, there are other crucial reasons to limit the transmission of pathogens: bacteria are sometimes able to swap genetic information with each other, across species. Many genetic determinants of antibiotic resistance are contained within mobile elements such as plasmids and integrons. When infected patients are cared for in clinics or hospitals, these genes may be transferred efficiently if hygiene protocols are breached. Even more alarming is the frequency with which this may happen in the built environment when sanitation practices are insufficient, and human effluent mixes together and then enters the water supply without proper treatment. Fortunately, simple interventions, such as hand hygiene by healthcare workers and the installation and use of proper pit latrines or flush toilets in austere settings, can have a huge impact.
- *Agricultural use of antibiotics*. The more selective pressure we assert on the microbiome, the more we accelerate the evolution of MDROs. According to the Food and Drug Administration (FDA), over 80% of antibiotics in the United States—more than 13 million kilograms annually—are given to livestock to promote growth or prevent infection. This practice has been associated with the development of MDR Gram-negative rods, such as fluoroquinolone-resistant *Campylobacter* species, which can be transmitted to humans via unsafe meat handling processes. These massive quantities of antibiotics may also enter the water supply, and then the human host, leading to unpredictable alterations in the gastrointestinal microbiome. Other nations have banned this practice, without suffering detrimental increases in the cost of producing poultry or beef. Whether the United States will reduce this practice from a regulatory perspective or whether market demands will lead to change remains to be seen.
- *Injudicious use of antibiotics in human medicine*. Although the use of antibiotics in humans is less than in animals in most industrialized nations, medical providers around the world bear a huge portion of the blame for our current predicament. Multiple expert reviews of large patient cohorts reveal a stubborn truth that has not changed appreciably over the decades: in general, 50% of antibiotic prescriptions are inappropriate (in terms of indication, spectrum, dose, or duration). The wise use of antibiotics is called "antimicrobial stewardship." All clinicians have important roles to play as good antimicrobial stewards. Resources are listed in the Further Reading section of this chapter. Fundamentals are included in **Table 29.1**.

PREVENTION OF MDRO INFECTION: THE TRAVELING PATIENT

MDRO infections are part of the reality of traveling abroad, and this topic should be included in pre-travel counseling. Core points to discuss with patients before leaving include the following:

- *Protect yourself without becoming a "germophobe."* Most of the toughest-to-treat MDROs acquired overseas are Gram-negative rods, from the family *Enterobacteriaceae*. In other

TABLE 29.1 Principles of Effective Antimicrobial Stewardship

- **Maintain Meticulous Infection Control.** Minimize the risk of passing resistance genes to bystander bacteria by keeping drug-resistant pathogens away from other patients—and yourselves. Clean hands before and after every encounter, obey other special precaution protocols, and maintain a clean examination area or hospital room.
- **Establish a Firm Diagnosis.** Is the patient truly infected with a bacterial pathogen? Some diseases mimic infection but do not respond to antibiotics. If bacterial infection is present, culture data are extraordinarily helpful, because they will reveal not only the pathogen but also its susceptibility profile. Ideally, cultures should be obtained before antimicrobials are started. But for patients who have a severe infection, delays in starting treatment may have grave consequences; start antibiotics immediately and send specimens for culture as soon as possible.
- **Say NO to Antibiotics for Viral Rhinosinusitis.** The common cold is due to viral infection approximately 95% of the time. Encourage patients to "get smart" about antibiotics, treat their symptoms, and emphasize the importance of maintaining the effectiveness of these medications if they should eventually require them.
- **Deescalate When Possible.** If broad-spectrum empiric treatment was initiated for severe infection, be willing to trust the results of positive cultures and focus treatment. More expensive, newer drugs may not be superior to tried and true therapies.
- **Shorter May Be Better.** Using the briefest duration of therapy possible may reduce selective pressure on bystander, normal flora. Subtherapeutic doses or intermittent, haphazard dosing are enormous mistakes, but treating at a full dose for a short period may have benefits for resistance—so long as the underlying infection has been adequately treated.
- **Collaborate with Experts.** Specialists in the field of infectious diseases medicine are always eager to collaborate with other physicians, both to generate protocols and to care for specific patients. Consult these specialists when patients are severely ill, when they fail to improve as expected, when the resistance profile is unexpectedly severe, or when treatment involves multiple or toxic drugs.

words, human fecal bacteria. Prevention of gastrointestinal illness is an excellent way to prevent gut colonization with these MRDOs. Hands should be cleaned before and after eating, and after using the lavatory, with soap, water, and a clean towel—or a hand rub containing at least 60% alcohol if this is not possible. Food should be chosen wisely, because of concern for contamination with human coliform bacteria introduced during preparation and storage. The mantra "Peel it, boil it, cook it, or forget it" is a fine start, but this may be difficult for patients to accomplish. The principles of smart eating and drinking habits are reviewed in depth in Chapters 7 and 8. Wearing a surgical mask when in public has a very small chance of preventing bacterial MDRO infections and is not usually recommended for this purpose.

- *Get all appropriate immunizations, including seasonal influenza.* Some bacterial MDRO infections may be directly prevented by immunizations (e.g., typhoid fever and pertussis). But the prevention of viral infections can also reduce the risk of MDRO bacterial infection, principally by reducing the likelihood of developing a febrile illness that might lead to healthcare interactions and inappropriate antibiotic use. Add this to the list of the many reasons why travelers should receive all appropriate vaccinations before leaving.
- *Avoid "medical tourism."* As the cost of surgical procedures seems to continue to rise in industrialized nations, some patients seek more affordable care overseas, particularly in Mexico, India, and China. Certainly, there are centers of excellence in these nations and elsewhere around the globe. Furthermore, post-procedural infections still happen in North America with unacceptable frequency. However, numerous case reports substantiate the concern that infection control and quality assurance overseas are often provided at a level below that achieved in Europe and North America. Patients may fail to grasp the impact—personal and financial—of healthcare infections acquired overseas. These can be dangerous, debilitating, disfiguring infections, and the cost of aftercare alone may meet

or exceed the savings envisioned. Thus, in general, planning trips for medical procedures should be discouraged. Seeking care for an acute medical problem while overseas is quite different, and patients should not be discouraged from seeing a healthcare provider if the need arises.

- *Use antibiotics wisely*. As described above, antimicrobial stewardship can have major impacts on public health; it can also benefit individual patients. Every prescription for antibiotics written pre-departure should come with clear guidance on when to initiate self-treatment during the trip. Patients who take antibiotics for uncomplicated secretory diarrhea put themselves at risk for *C. difficile* infection, prolongation of symptoms due to altered microbiota ("antibiotic-associated diarrhea"), and development of de novo antibiotic resistance within their own native bacteria. For this reason—among others—antibiotics should not be taken as "routine prophylaxis" but rather reserved for the unusual occurrence of high-risk infections, such as dysentery, except in exceptional cases as described in Chapter 8.
- *Quit smoking*. Most smokers acknowledge that their addiction is hazardous to their health, and are interested in quitting. Here is another motivator: respiratory infections are more frequent among smokers, and thus they are more susceptible to MRDOs; they also require antibiotics more often, which in turn puts them at even higher risk of creating new MDROs in their own bodies.
- *Practice safe sex*. Certain bacterial sexually transmitted diseases (STDs), such as gonorrhea, are becoming more and more drug resistant over time and may require higher doses, longer courses, and parenteral routes of therapy (see Chapter 42). Pre-travel safe sex counseling should pay dividends in terms of preventing acquisition of MDRO STDs.
- *Probiotics are probably safe but of unproven benefit*. The "health-savvy" patient may seek your advice on probiotics. The concept is attractive: use friendly microbes to keep the bad ones at bay. Published studies to date vary in terms of design—different settings, different interventions, and different outcome measures. Recent meta-analyses suggest a trend toward benefit in the treatment arms, but rarely a large enough benefit to achieve statistical significance. Given the complexity of our gastrointestinal microbiomes, it is small wonder that taking megadoses of one or a few microbes fails to reliably set things to right, including prevention of traveler's diarrhea. Further complicating the issue is a lack of ingredient standardization or regulatory oversight by the FDA for these products, which are classified as dietary supplements rather than medications. On the other hand, probiotics are unlikely to harm the patient—unless he or she has a suppressed immune system, in which case the probiotic microbes can become invasive, leading to colitis or bloodstream infection. In summary, patients should be told that the jury is still out, but for those with a healthy immune system it is reasonable to add once- or twice-daily probiotic supplements to their diets while abroad, although this is not a substitute for any of the other interventions outlined above.

RECOGNITION AND MANAGEMENT SUGGESTIONS FOR MDRO INFECTIONS

Because most bacteria have the potential to become MDROs, and because they can infect virtually any part of the body, a comprehensive discussion of the clinical presentation and management of these infections is beyond the scope of this chapter. However, advice regarding the most common MDRO syndromes in returning travelers includes discussions about the following:

- *Silent colonization*. Conceptually, when a germ comes into contact with a human being, one of four things happens: the two simply ignore each other; the germ kills the host; the host kills the germ; or an agreement is reached—a state referred to as "colonization." In colonization, bacteria inhabit an ecological niche within the patient, such as body hair follicles, the anterior nares, the oropharynx, the lower gastrointestinal tract, or the genitourinary tract. By definition, colonizers are clinically silent and cause no signs or symptoms of disease. However, colonizers can become pathogens in a moment, if given the opportunity by the host. This could happen with waning humoral immunity (as during

chemotherapy), impaired cellular immunity (as in untreated human immunodeficiency [HIV] infection), anatomical injury (as in surgical wound infections), or alteration of the competitors within an ecological niche (as in antibiotic-associated diarrhea). Surveillance data are lacking, but clinical experience suggests that many patients who acquire MRDOs while overseas have asymptomatic colonization of the gastrointestinal tract. By itself, this is harmless; however, if these germs are allowed to flourish under the selective pressure of antibiotics, or if they migrate to other anatomic sites, then infection may develop. MDRO colonization may last for days, years, or anything in between. Patients who have traveled overseas for any considerable period of time, especially those who received health care during the trip, are at elevated risk for gastrointestinal MDRO colonization for at least the first 6 months after return. However, this is an arbitrary number, and there are many cases in which patients have demonstrated sustained colonization years after their exposure. This may have implications for infection control in the hospital or clinic. Currently there is no national consensus on whether to look for asymptomatic MDRO colonization, for example, via a rectal swab or fecal culture, in part because of the challenges this poses in the laboratory, and because it is not entirely clear what to do with that information. It may be simpler to assume these patients are colonized, and thus to treat them using contact precautions (diligent hand hygiene, gowns, and gloves). However, it is reasonable to consider surveillance cultures as part of a comprehensive infection control strategy if your clinic or center encounters these organisms frequently.

- *Gastrointestinal infection*. The gastrointestinal tract is a leading reservoir for MDRO colonization, although invasive infection is relatively uncommon. As described in Chapters 21 and 30, enteric fever due to *Salmonella enterica* serovars *typhi* and *paratyphi* are leading causes of fever among travelers returning from the tropics. In the past, fluoroquinolones such as ciprofloxacin and levofloxacin were reliable treatment options for these infections; currently, the majority of isolates acquired in Southeast Asia, in particular South Asia, are partially or fully resistant to fluoroquinolones. Third-generation cephalosporins such as ceftriaxone are more reliable empiric choices and can be used in uncomplicated disease, but unfortunately resistance to this class is also on the rise. Someone who is septic with suspected salmonella infection acquired in India should be admitted and treated empirically with a carbapenem such as ertapenem, until antibiotic susceptibility testing confirms a narrower-spectrum agent can be used. Similarly, enterotoxigenic *E. coli* (ETEC), which was once predictably susceptible to fluoroquinolones, is increasingly resistant—again particularly in Southeast Asia—and alternative drugs such as azithromycin are more reliable today. Other MDR Enterobacteriaceae, including carbapenem-resistant species, may require toxic agents such as aminoglycosides for treatment. Fortunately, symptomatic infection of the gut is uncommonly caused by carbapenem-resistant Enterobacteriaceae, presumably because these bacteria infrequently carry extra virulence genes. Drug resistance and increased virulence are not necessarily found together.
- *Urinary tract infection* (*UTI*). MDR Gram-negative rods, especially from the Enterobacteriaceae group, which includes *E. coli*, may be detected in the urine of returning travelers, particularly women. Presumably, this is because gastrointestinal colonization is a common source of MDROs in travelers (see above), and proximity of the urethral meatus to the anal aperture facilitates bacterial entrance into the urinary tract (just as happens with all UTIs). Because treatment can be challenging, it is essential to distinguish between true UTI and asymptomatic bacteriuria (ABU). If a patient does not have signs or symptoms of UTI such as urinary urgency or frequency, hematuria, pyuria, suprapubic tenderness, or an abnormal urinalysis, or if her urine was tested for reasons that are unclear, then by definition she has ABU, which should *not* be treated with antibiotics. On the other hand, if clinical suspicion for true UTI is high, then treatment is appropriate. Guidelines of the Infectious Diseases Society of America suggest that uncomplicated UTI be treated empirically, without sending a urine culture unless symptoms persist or recur. However, patients who have recently been overseas may not fit into this category of "uncomplicated," and

our practice is to send a clean-catch midstream urine specimen for urinanalysis and reflexively for culture if the urinanalysis is abnormal at the first presentation for these patients. Culture data will take time, however, so an empiric prescription will be necessary. Ideally, these patients should receive one dose of fosfomycin 3 gm PO, because resistance to this drug is less common than to the alternative first-line treatments (trimethoprim-sulfamethoxazole 1 dose PO BID for 3 days or nitrofurantoin 100 mg PO BID for 5 days). Alternative oral treatments are even less likely to succeed against MDR Enterobacteriaceae, such as ciprofloxacin or cefpodoxime.

After culture and resistance data are available, empiric treatment can be changed if the patient has failed to improve. In many cases, no oral treatment will have a favorable in vitro resistance profile. This is an appropriate situation in which to consult a specialist in infectious diseases, who may have access to experimental oral treatments or who can assist with parenteral treatment if indicated. In many cases, an intravenous course of a carbapenem, such as ertapenem 1 gm IV daily for 5 days, may be required.

Some patients will develop recurrent UTI symptoms, which can be stubborn and frustrating for everyone. An emerging strategy that may hold promise involves resetting the microbiome of the vagina. *E. coli* does not belong in the vagina in substantial amounts, and most UTIs in otherwise healthy women are caused by *E. coli* ascending the urethra from the introitus. A leading hypothesis is that the vagina is usually protected from high-level *E. coli* colonization because of its low pH, which is provided by the activity of human lactobacilli, including *Lactobacillus crispatus* and *Lactobacillus iners*, among other species. These healthy bacteria may be wiped out inadvertently by antibiotic courses given for other reasons, such as rhinosinusitis. Sadly, most commercially available lactobacillus supplements contain bovine species such as *Lactobacillus rhamnosus*, which do not lower vaginal pH appropriately. Fortunately, clinical trials of human lactobacilli in vaginal suppositories have shown a protective effect, and there is hope that FDA registry trials will result in approval of this product in the near future. If so, it would be appropriate to offer this technique to patients with recurrent UTI (regardless of their bacterial resistance profile). This is also yet another reason to prescribe antibiotics prudently, to prevent altering the vaginal microbiome in the first place. Patients who ask for antibiotics for inappropriate indications may respond to this teaching by their physician.

- *Skin and soft tissue infections*. In developed nations, the origin of skin and soft tissue infections is relatively predictable: cellulitis without purulence is usually caused by streptococcal species (including Group A beta-hemolytic *Streptococcus pyogenes*), whereas purulent infections such as "boils," furuncles, carbuncles, and abscesses are usually caused by *Staphylococcus aureus* (both methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus*). In a returning traveler, this pattern remains accurate (see Chapter 36). However, other pathogens should be considered as well, depending on host factors and environmental exposures. Providers must obtain a careful, detailed history in order to avoid missing drug-resistant bacterial infections. For example, the risk of MDR Gram-negative skin infections is greatly increased among patients who have undergone surgical procedures overseas or who sustained a wound exposed to fresh water. Such wounds may have become infected by environmental organisms such as *Acinetobacter*, *Pseudomonas*, *Aeromonas*, *Burkholderia*, and rapidly growing mycobacteria, which can be profoundly resistant to most, if not all, antibiotics. Thus, an interdisciplinary approach is required for these patients: there should be a low threshold to admit severely infected patients to the hospital (with full and aggressive contact precautions). There, tissue and blood specimens should be submitted for culture and sensitivity testing, and consultation should be sought from specialists in both infectious diseases (because toxic medications may be necessary, such as aminoglycosides, polymyxins, or tigecycline) and surgery (because in some cases rapid debridement or even amputation may be life-saving).
- *Respiratory infections*. Infections of the lung and respiratory tract among returning travelers are second only to gastrointestinal infections. The great majority are either presumed or proven to be caused by viruses (e.g., *influenza*, *parainfluenza*, *rhinovirus*, or *coronavirus*).

These infections may be "garden variety" or novel forms acquired during travel, such as highly pathogenic avian influenza (HPAI) or Middle East respiratory corona virus. Furthermore, these viral processes may mask, mimic, or predispose patients to drug-resistant bacterial infections. For example, *S. aureus* or *Haemophilus pneumoniae* infections may follow influenza infection. So-called atypical bacterial pneumonia due to *Legionella* or *Chlamydia* may have a clinical and radiographic appearance that looks very much like viral pneumonia. These infections require early detection and antibiotic coverage in order to prevent substantial risk of morbidity and mortality. All physicians know well the principle of "Occam's razor," in which the single answer with the fewest uncertainties should be selected. This is usually a wise approach in infectious diseases medicine; however, because there are so many microbes that threaten people in austere settings, multiple infections may present simultaneously or in close sequence. Thus, caution should be advised in the ill traveler returning from the tropics, where "Occam's razor may grow rusty in the humid atmosphere," so to speak.

FURTHER READING

Center for Disease Dynamics, Economics and Policy. <www.CDDEP.org>.
Website maintained by the CDDEP, an independent, not-for-profit organization dedicated to collection and dissemination of information regarding antimicrobial resistance.

Centers for Disease Control and Prevention. <www.cdc.gov/GetSmart>.
User-friendly website maintained by the CDC, including patient-oriented information on the importance of wise antibiotic use.

Dellit, T.H., Owens, R.C., McGowan, J.E., Jr., et al., 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin. Infect. Dis. 44 (2), 159–177. PMID: 17173212.
State-of-the-art guidelines on how to set up an antimicrobial stewardship program from the Infectious Diseases Society of America.

Shepherd, A.K., Pottinger, P.S., 2013. Management of urinary tract infections in the era of increasing antimicrobial resistance. Med. Clin. North Am. 97 (4), 737–757. PMID: 23809723.
Practical advice for medical providers regarding strategies for dealing with urinary tract infections due to MDROs.

World Health Organization. <www.who.int/drugresistance>.
Clearinghouse of information regarding the global burden and epidemiology of antibiotic resistance, maintained by the WHO.