CHAPTER 97

# Principles of Antibiotic Prescription in Intensive Care Unit Patients and Patients With Acute Renal Failure

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**OBJECTIVES**

This chapter will:

1. Review basic principles of antibiotic prescribing.
2. Discuss the implications of the emergence of multi–drug-resistant organisms.
3. Review the mechanisms for antibiotic resistance.

Intensive care units (ICUs) are unique because they provide confined accommodations for the critically ill patient, where antibiotic use is extremely common. They are often the center of infections; it is estimated that 37% to 51.2% of all ICU patients are treated for infection during their stay.[1] This increased risk is secondary to the extreme vulnerability of its population; the use of multiple procedures, each with a high potential for infection; and the use of invasive devices distorting the anatomic integrity-protective barriers of patients. In addition, several drugs may be administered that also predispose for infections such as pneumonia (e.g., by reducing the cough and swallow reflexes [sedatives, muscle relaxants]) or distort the normal nonpathogenic bacterial flora (e.g., stress ulcer prophylaxis).

It has been estimated that more than 20% of all nosocomial infections occur in the ICU.[2,3] In the setting of these nosocomial infections, antimicrobial resistance has emerged as a major concern and an important determinant of outcomes for patients in the ICU. This is largely secondary to the use of inappropriate antibiotics in the increasing presence of organisms that are resistant to current antibiotics. In a study looking at 2000 ICU patients, inadequate antibiotic therapy for nosocomial infections in the ICU occurred in 8.5% and had an associated mortality of 52.1%.[4] According to the EPIC II 1-day prospective point-prevalence study (Extended Prevalence of Infection in Intensive Care) in 1265 participating ICUs (75 countries worldwide), 51% of the 12,796 patients were considered infected, although no subdivision was made for hospital-acquired infections.[5] The pathogens that are causing these infections may be intrinsically resistant to antibiotics but also can cause resistance by inducing or evolving resistance. This has major implications for healthcare in general and particularly in the ICU, where resistant organisms can present major challenges because patients tend to be debilitated and particularly susceptible to nosocomial infection. Such infections often

lead to prolonged ICU and hospital stay and consequent increased healthcare costs.

## PATHOGENS OF CONCERN: MULTI-DRUG–RESISTANT ORGANISMS

Multi-drug–resistant (MDR) organisms are microorganisms that have become resistant to multiple antibiotics. Infection resulting from MDR organisms in critically ill patients presents particular challenges to clinicians, given the lack of a pipeline of new antibiotics active against these resistant strains. MDR organisms are often the etiologic agents with a dramatic impact on morbidity and mortality rates. Drug-resistant pathogens pose tremendous challenges to the healthcare system, including challenges related to the diagnosis, treatment, and containment of infections caused by resistant organisms.[6,7] These challenges are amplified in the ICU, where the threat of potential drug resistance is one of the major drivers for the selection of empiric antimicrobial regimens. There are not only pressures for selection and emergence of resistance of these organisms but also the highest risks of transmission of drug-resistant pathogens.[8]

Over the past decades, the MDR organisms are shifting from gram-negative from gram-positive bacteria.[9,10] This transition likely is due to the shortage of new antimicrobial agents active against gram-negative organisms. Among gram-negative organisms, the resistance is due mainly to the rapid increase of extended-spectrum β-lactamases (ESBLs) in *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis*; high level third-generation cephalosporin β-lactamase resistance among *Enterobacter* spp. and *Citrobacter* spp., and MDR in *Pseudomonas aeruginosa, Acinetobacter* spp., and *Stenotrophomonas maltophilia.*[11] Across ICUs, the most important resistant microorganisms in the ICU are currently methicillin-resistant *Staphylococcus aureus*, (MRSA) and vancomycin-resistant enterococci (VRE). Other important organisms include *Clostridium difficile, Streptococcus pneumoniae,* and *Candida* spp.

## TREATMENT

Clinicians now face a difficult decision of when to start antibiotic therapy in the ICU in the setting of increased prevalence of MDR organisms in the ICU. The dilemma the healthcare worker has to face is the increasing rates of MDR organisms countered by the overuse of antibiotics and the morality benefit of starting prompted antibiotic therapy in this setting. When antibiotic therapy is initiated, three requirements must be fulfilled. First, the antimicrobial agent(s) should be initiated as soon as possible after the onset of sepsis.[12] Second, because therapy is to be initiated empirically, the antimicrobial spectrum of the agent should be broad enough to cover the potential causative microorganisms.[13] Finally, appropriate antimicrobial dosing is required to maximize microbial killing, minimize the development of multi-drug antimicrobial resistance, and avoid concentration-related adverse drug reactions.[14–16] It has been well documented that a delay in starting antibiotic therapy or starting inappropriate antibiotic therapy, when treating pneumonia or bloodstream infections, can lead to increased mortality.[3,17,18] When there is a delay in starting antibiotics in a patient with septic shock, there is an associated increase in morality.[12] Therefore in a critically ill patient in the ICU with suspected or documented infection, empiric antibiotic therapy should be instituted.

Optimizing antimicrobial dosing for critically ill patients is highly challenging, and failure to achieve it can lead to worse patient outcomes. These patients often have decreased renal clearance, hepatic clearance, increased volume distribution, and low albumin, which can affect the pharmacokinetics (PK) of antibiotic therapy. Use of dosing regimens recommended in package inserts from drug manufacturers is frequently insufficient to guide dosing in these patients appropriately. Although the effect of critical illness pathophysiology on the PK behavior of antibiotic therapy can be profound, the variability of these changes between patients still is being quantified. The PK effects of hypoproteinemia, organ dysfunction, and the presence of augmented renal clearance may lead to plasma antibiotic concentrations that are difficult to predict at the bedside. This may result in excess toxicity, especially in the ICU patient. More importantly, insufficient antibiotic therapy exposure leads to the development of antibiotic resistance as well as likely worse outcomes. The dosing of antibiotic therapy in critically ill patients with suspected or documented infection should be personalized to achieve optimal concentrations and higher doses according to the DALI (Defining Antibiotic Levels In Intensive Care Patients) study.[19]

In selecting the appropriate antibiotics, clinicians have to take into account that patients in the ICU usually have severe comorbid conditions and more frequently undergo invasive procedures and are on mechanical ventilation. Most of the infections that occur in these patients are life threatening and are caused by gram-negative organisms that are resistant to multiple antibiotics. Prior studies demonstrated a survival benefit to empiric antibiotic therapy that is prompt and broad, covering gram-positive and gram-negative organisms. Thus the first therapeutic principle is to give prompt, aggressive, broad-spectrum, and adequate initial empirical therapy for serious infection and to de-escalate the treatment according to the results of antibiotic susceptibility data.[20]

To optimize antibiotic therapy in serious infection, combination therapy appears to be an acceptable option. Combination therapy is used extensively in infectious diseases to enhance the cure of infection and prevent the development of resistance. This therapy is used is the case of antiretroviral combination therapy that has revolutionized the treatment of HIV infection, the treatment of tuberculosis, *Helicobacter pylori* infection, and in enterococcal endocarditis.[21] Combination therapy works because of the synergistic effect, which is based on in vitro observations. It also believed that combination therapy should prevent the emergence of resistant bacteria in the course of antibiotic exposure.

In critically ill patients in the ICU, combination therapy offers a potentially valuable option for MDR gram-negative organisms. However, there are controversies regarding whether synergistic antibiotic combinations could improve the patient's outcome and prevent the emergence of resistance.[21] The main controversy is the lack of randomized, controlled studies, including an adequate population size. Indeed, there are many variables such as time of initiation of antibiotic treatment, adequacy of empiric treatment, polymicrobial infections, adverse events, superinfections, and underlying diseases, all of which can affect the outcome as well.

In a meta-analysis of 64 trials, which included 7586 patients, comparing β-lactam monotherapy with β-lactam

and aminoglycoside combination therapy for severe infections, researchers found no difference in all-cause fatality (relative risk: 0.90; 95% CI: 0.77–1.06).[22] Also, the Cochrane analysis, which was reviewed by Paul et al., compared clinical outcomes of β-lactam and aminoglycoside combination therapy versus β-lactam monotherapy for sepsis. In their analysis, they found that the addition of an aminoglycoside to β-lactams for sepsis was ineffective, because all-cause fatality rates were unchanged, and the combination therapy with aminoglycosides carried a significant risk of nephrotoxicity.[23] In a number of other trials, there was no evidence of any potential prevention of infection resulting from resistant isolates with combination therapy. Overall, 41 randomized trials comparing 29 unique regimens were found, and no mortality differences were observed between any of the regimens compared.[24] Because multiple clinical studies have not demonstrated any survival benefit in using combination therapy and the exposure of more than one class of antibiotics may increase the risk of transmission of MDR organisms, combination therapy to treat empiric gram-negative organisms should be used carefully on a case-by-case basis. One exception, in which combination therapy would be warranted, is in the treatment of carbapenem-resistant Enterobacteriaceae infections.[25–27] Factors the clinician should take into account when choosing empiric antibiotic therapy include prior antibiotic exposure, prior organisms causing infection, and the sensitivity pattern and antibiogram of the ICU.

## EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE IN THE INTENSIVE CARE UNIT

In many hospitals around the world, antibiotic resistance has become an increasing crisis. In the ICU gram-positive organisms, especially MRSA, and many gram-negative organisms cause these infections.

Gram-positive infections are identified primarily as *S. aureus* and *Enterococcus* species. In the ICU the majority of them are identified as MRSA and VRE. The therapeutic options in treating these resistant gram-positive organisms include vancomycin, linezolid, daptomycin, tigecycline, quinupristin-dalfopristin (Synercid), telavancin, and ceftaroline. A summary of the treatment choice, dose, and common side effects is in Table 97.1.

Two important MDR isolates of *S. aureus* include vancomycin-intermediate *S. aureus* (VISA), defined as a minimum inhibitory concentration (MIC) of 4 to 8 μg/mL, and vancomycin-resistant *S. aureus* (VRSA), defined as a vancomycin MIC of at least 16 μg/mL. The first documented infection with VISA was reported in a patient in Japan in May 1996. Subsequently, infections with VISA strains have been reported in patients from the United States, Europe, and Asia. All VISA examined have had nontransferable resistance mechanisms, which are not maintained in the absence of vancomycin. VISA are considered less of a public health threat than VRSA; however, VISA is still clinically important, and laboratories should ensure that treating physicians and infection control are notified of VISA per facility policy.

As of May 2015, 14 VRSA infections have been reported in patients from the United States. All VRSA described to date have acquired the vanA vancomycin resistance gene and operon, commonly found in VRE. When VRSA is identified in a clinical laboratory, laboratory personnel immediately should notify the patient's primary caregiver, patient care personnel, and infection control so that appropriate infection control precautions can be initiated promptly. Notifying local and state public health departments is also important. These notifications should occur while waiting for VRSA confirmatory testing.

Another gram-positive infection that has developed resistance is streptococcal pneumonia. Most pneumococcal infections are community acquired, but pneumococcal meningitis, bacteremia, and pneumonia are common causes of admission to an ICU. Data from the CDC Active Bacterial Core Surveillance Program in 2009 shows continued declines in pneumococcal susceptibility to multiple antibiotics classes, including penicillins, third-generation cephalosporins, erythromycin, and trimethoprim- sulfamethoxazole.[28] Resistance is classified as intermediate or high level; high-level resistance cannot be overcome by increasing drug doses and leads to treatment failure, especially for meningitis. High-level penicillin resistance indicates resistance to all penicillins and to first- and second-generation cephalosporins. Decline in the rate of drug resistance *S. pneumoniae* among invasive pneumococcal isolates was observed after introduction of the 7-valent conjugate pneumococcal vaccine, although trends have reversed as new drug-resistant Streptococcus pneumoniae (DRSP) serotypes have become more prevalent. Additional resistant serotypes are targeted in newer conjugate vaccines.

Penicillin-resistant pneumococci are often resistant to other drugs, including macrolides, clindamycin, tetracyclines, and trimethoprim-sulfamethoxazole. Choice of therapy includes fluoroquinolones, with rare resistance described at 0.03% to levofloxacin[28] and vancomycin. Vancomycin resistance in *Pneumococcus* spp. is not reported, although tolerance to vancomycin killing has been described.[29]

Infections caused by gram-negative organisms in the ICU are often MDR organisms. These organisms include common MDR Enterobacteriaceae (ESBL-producing *Klebsiella* species and *Escherichia coli*, AmpC-producing β-lactamase *Enterobacter* species, *Citrobacter freundii, Serratia marcescens,* and *Morganella morganii*, and carbapenemase-producing mostly *Klebsiella* species and *E. coli* but other Enterobacteriaceae) and common MDR nonfermenting gram-negative bacteria *(P. aeruginosa, Acinetobacter baumannii,* and *S. maltophilia).* The therapeutic options in treating these resistant gram-negative organisms include carbapenem, tigecycline, high-dose ampicillin-sulbactam, colistin, fluoroquinolone, aminoglycosides, ceftaroline, ceftazidime-avibactam, ceftolozane-tazobactam, and fosfomycin. A summary of the treatment choice, dose, and common side effects is given in Table 97.2.

In the planning strategic treatment of ventilator-associated pneumonia (VAP), the adjuvant use of inhaled antibiotics should be considered in treating MDR organisms. Many recent observational and small, randomized trials have shown encouraging results with decreased toxicity using adjunctive inhaled therapy with aminoglycosides or colistin for treatment of VAP caused by gram-negative MDR organisms.[30,31]

Other organisms of concern include *C. difficile* and *Candida* infections. Increasing concerns about *C. difficile* further complicate the choice of antibiotic. These organisms are among the most difficult microorganisms to eradicate in the environment.[32] Antiseptics cannot destroy the spores of *C. difficile*; therefore handwashing with water and soap is essential to eradicating the carry of the spore from one area to the next. Disease severity ranges from mild diarrhea to fulminant pseudomembranous colitis; *Clostridium* spp. are actually responsible for almost all antibiotic-associated pseudo-membranous colitis.[33] Several outbreaks have been described, leading to an increase in the incidence. The

**TABLE 97.1**

**Resistant Gram-Positive Organisms and Treatment**

| ANTIBIOTICS | ACTIVITY AGAINST RESISTANT BACTERIA | INTENDENT SITES OF TREATMENT | COMMON SIDE EFFECTS |
|---|---|---|---|
| Vancomycin | MRSA, *S. pneumoniae* | All sites | Red man syndrome-related to infusion rate, hypotension accompanied by flushing, reversible neutropenia, nephrotoxicity, ototoxicity (especially with large doses), thrombocytopenia |
| Daptomycin | MRSA, VRE (Faecium only) | All sites, except pneumonia | Myopathy, drug rash with eosinophilia and systemic symptoms (DRESS) |
| Linezolid | MRSA (including VISA/VRSA),VRE (Faecium and Faecalis) | | Bone marrow suppression, peripheral nephropathy, lactic acidosis |
| Quinupristin-dalfopristin (Synercid) | VRE (Faecium only) | Skin and skin structure infections | Myalgias, arthralgias |
| Tigecycline | MRSA, *S. pneumoniae,* VRE (Faecium and Faecalis) | Complicated skin and skin structure infections, complicated intra-abdominal infections, and CAP. Not indicated for the treatment of HAP or VAP. | Nausea, vomiting |
| Ceftaroline | MRSA (including VISA/VRSA), *S. pneumoniae* | Skin and skin structure infections, CAP, BSI, endocarditis | Diarrhea, nausea, rash |
| Telavancin | MRSA (including VISA/VRSA), *S. pneumoniae,* VRE (Faecium and Faecalis) | Skin and skin structure infections, HAP, VAP, BSI | Nephrotoxicity, nausea, vomiting, reproductive toxicity |
| New glycopeptides<br>Oritavancin<br>Dalbavancin | MRSA | Skin and skin structure infections | Nausea, headache, vomiting, diarrhea, increased ALT/AST, dizziness, infusion site phlebitis, tachycardia |
| Tedizolid | MRSA (including VISA/VRSA),VRE (Faecalis only) | Skin and skin structure infections | Nausea, vomiting, headache, diarrhea, anemia, thrombocytopenia, visual disturbances, infusion-related reactions |
| Gentamicin | Administered in combination with ampicillin or vancomycin | Provides bactericidal activity for treatment of enterococcal endocarditis and other serious enterococcal infections | Nephrotoxicity, ototoxicity |

In a comparative clinical trial, greater mortality and decreased efficacy were reported in tigecycline -treated patients.
*ALT,* aspartate transaminase; *AST,* alanine transaminase; *BSI,* bloodstream infection; *CAP,* community-acquired pneumonia; *HAP,* hospital-acquired pneumonia; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *VAP,* ventilator-associated pneumonia; *VRE,* vancomycin-resistant Enterococcus; *VISA,* vancomycin intermediate *S. aureus*; *VRSA,* vancomycin-resistant *S. aureus.*

misuse of particular antibiotics such as cephalosporin and quinolones are thought to be the leading cause of the development and dissemination of strains with increased virulence and failures in basic infection control strategies.[34]

The management of treating *C. difficile* includes immediate isolation and confirmation of cases with stool sample toxin assays. Treatment is preferably with oral antibiotics metronidazole or vancomycin. If patients cannot take anything orally, then metronidazole is given intravenously, although it is a less efficacious alternative. One concern in the reduced susceptibility to metronidazole, antibiotic treatment also becomes more difficult.[35] For severe *C. difficile* oral vancomycin and intravenous metronidazole should be used. For treatment failure or recurrent disease other interventions have been used, which include vancomycin enemas, fecal microbiota transplant (FMT), and diverting colostomy.[36]

Patients in the ICU are at risk of invasive candidiasis as a result of their immunocompromised status. Candidiasis is the leading cause of fungal infections in ICU patients and is an important cause of morbidity and mortality in these critically ill patients. The issue with *Candida* infection is that, although *C. albicans* is still the most common causative agent, there is an increase in infections with two important non-*albicans* spp. These organisms are intrinsically fluconazole-resistant *Candida krusei* or the dose-dependent susceptible *Candida glabrata.*[37]

There are several risk factors for the development of invasive disease, such as the colonization of the gastrointestinal tract, disruption of the mucosa, neutropenia or immunosuppression, the increased use of medical procedures, and poor hygiene of the healthcare personnel.[38] Undoubtedly, the early diagnosis and treatment of invasive candidiasis is important but is often not an easy task because of the comorbidities and the delay in obtaining positive cultures. Blood cultures have a sensitivity of up to 70%, but they have a long incubation time and they are often negative in deepseated candidiasis and when fluconazole

**TABLE 97.2**

**Resistant Gram-Negative Organisms and Treatment**

| ANTIBIOTICS | ACTIVITY AGAINST RESISTANT BACTERIA | INTENDENT SITES OF TREATMENT | COMMON SIDE EFFECTS |
|---|---|---|---|
| Carbapenems | MDR *Pseudomonas* spp., ESBL | All sites | Nausea, diarrhea, headache, seizure |
| High-dose ampicillin-sulbactam | Activity against MDR *A. baumannii* only | All sites | Phlebitis/thrombophlebitis, nausea, vomiting, headache, anaphylaxis-PNC allergy |
| Colistin | Activity against MDR *Acinetobacter, Pseudomonas*, CRE, KPC (does NOT have activity against *Proteus, Serratia, Providentia, Burkholderia, Stenotrophomonas*) (use as combination therapy) | All sites as combination therapy | Nephrotoxicity, neuromuscular blockade, neurotoxicity |
| Fluoroquinolone | MDR *Pseudomonas* spp, ESBL | All sites | Nausea, vomiting, dizziness, peripheral neuropathy, tendinopathy, QT-interval prolongation |
| Tigecycline | Activity against MDR GN organisms (no activity against *Proteus* spp. and *Pseudomonas aeruginosa*) | Complicated skin and skin structure infections, complicated intraabdominal infections, and CAP. Not indicated for the treatment of HAP or VAP | Nausea, vomiting |
| Ceftaroline | Activity against GN organisms. (No activity against *Pseudomonas* spp. or *Acinetobacter* spp. or gram-negative anaerobes) | Skin and skin structure infections, CAP | Diarrhea, nausea, rash |
| Aminoglycosides | Activity against MDR *Acinetobacter, Pseudomonas*, CRE, KPC (does NOT have activity against *Proteus, Serratia, Providentia, Burkholderia, Stenotrophomonas*) (use as combination therapy) | All site as combination therapy | Nephrotoxicity, ototoxicity |
| Fosfomycin (PO formulation in the US only, therefore minimal use in the ICU) | Activity against *E. coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., and VRE. (It does not have activity against *Acinetobacter* spp.) | UTIs (MDR GN organisms or patient with multiple allergies) | Nausea, diarrhea, headache, dizziness, asthenia, dyspepsia |
| Ceftazidime-avibactam | Enterobacteriaceae, including ceftazidime-resistant strains. (activity against *P. aeruginosa* is variable because of the potential presence of other resistance mechanisms in addition to β-lactamase production) (Synergy was observed for avibactam with ceftazidime in the *Burkholderia cepacia* complex) | cIAI (used in combination with metronidazole), cUTI (including pyelonephritis), used for CRE or KPC pneumonia off label | Nausea, vomiting, dizziness, increased blood alkaline phosphatase, increased alanine aminotransferase; anaphylaxis-cephalosporins |
| Ceftolozane-tazobactam | Activity against GN organisms and some strains of multi-resistant *Pseudomonas* spp. (It does NOT have activity against carbapenemase-producing Enterobacteriaceae.) | cIAI, cUTI, used for MDR *Pseudomonas* spp. Pneumonia off label | Nausea, vomiting, dizziness, headache, diarrhea, constipation, insomnia, increased ALT/AST, anaphylaxis-cephalosporins |

Ertapenem: No activity against *Pseudomonas* spp. or *Acinetobacter* spp.
*cIAI,* Complicated intraabdominal infections; *CRE,* carbapenem-resistant Enterobacteriaceae; *cUTI,* complicated urinary tract infections; *GN,* gram-negative; *KPC, Klebsiella pneumoniae;* MDR, multi-drug–resistant; *PCN,* penicillin.

prophylaxis is used. Serologic tests using components of the fungal cell wall such as galactomannan and 1,3-β-d-glucan or antibodies against galactomannan antigen are specific but they lack in sensitivity. One useful tool that is widely used, the *Candida Colonization Index* (CCI), is defined as the ratio of the number of culture-positive surveillance sites for *Candida* spp. over the number of sites cultured. If the CCI is greater than 0.4, preemptive antifungal therapy should be initiated.[39]

In addition, a recent study presented the Candida score (CS), which is based on the following risk factors: surgery upon admission, total parenteral nutrition, severe sepsis, and multifocal colonization. A CS above 2.5 identifies high-risk patients who may benefit from antifungal prophylaxis treatment.[40] European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines suggest the use of echinocandins (caspofungin, anidulafungin, micafungin) as the first-line therapy for empiric therapy, especially in unstable patients.[41] Current IDSA guidelines suggest the use of fluconazole in stable patients but in patients who have been exposed to fluconazole or unstable patients, then echinocandins or amphotericin B or its lipid formulations should be used in empiric therapy.[42]

## MECHANISMS FOR ANTIBIOTIC RESISTANCE

Over time, organisms in the presence of antibiotics have developed the mechanisms required to render the antimicrobial agent ineffective. The development of antibiotic resistance in particular stems from the drugs targeting only specific bacterial molecules. Because the drug *is* so specific, any mutation in these molecules will interfere with or negate its destructive effect, resulting in antibiotic resistance. In fact, several different mechanisms may work together to confer resistance to a single antimicrobial agent.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are the following:

1. The inactivation or modification of the antibiotic
2. An alteration in the target site of the antibiotic that reduces its binding capacity
3. The modification of metabolic pathways to circumvent the antibiotic effect
4. The reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing active efflux of the antibiotic

The development of resistance is inevitable after the introduction of a new antibiotic. These mechanisms can occur as a single mechanism or in combination within various bacteria. These mechanisms are summarized in Table 97.3.

Antibiotic resistance in bacteria can be described in two different ways. An inherent trait of the bacteria can cause it to be naturally or intrinsically resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source.

In a natural resistance bacteria may be inherently resistant to an antibiotic. Examples of this include that an organism lacks a transport system for an antibiotic; that an organism lacks the target of the antibiotic molecule; or the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic, in the case of gram-negative bacteria. Although some bacteria can have a natural resistance, most bacteria develop an acquired resistance. When a bacterium develops acquired resistance, several mechanisms are developed by bacteria to acquire resistance to antibiotics. All require either the modification of existing genetic material or the acquisition of new genetic material from another source. The most common acquired resistance is the uptake of exchromosomal DNA such plasmids, transposons, or integrons that contain antibacterial-resistant genes.

**TABLE 97.3**

**Mechanisms for Antibiotic Resistance**

| MODE OF RESISTANCE | ANTIBIOTICS |
|---|---|
| Enzyme production | Aminoglycosides<br>Amphenicols<br>Antifolates<br>β-lactams<br>Glycopeptides<br>Rifamycins |
| Target site modification | Aminoglycosides<br>β-lactams<br>Fluoroquinolones<br>Glycopeptides<br>Macrolides<br>Rifamycins<br>Tetracyclines<br>Linezolid |
| Structural changes to cell wall, protein channels, or transporters | Glycopeptide-resistant<br>Fluoroquinolones |
| Efflux pumps | Aminoglycosides |
| Development of alternate pathways or targets | β-lactams<br>Macrolides<br>Quinolones<br>Tetracyclines<br>Sulfonamides<br>Trimethoprim |

## PREVENTION

Because the pipeline of new antibiotic therapy is running dry,[9] the use of preventive measures is very important in prevailing over MDR organisms.

Practical measures to help prevent MDR infections include the following:

- Strict infection control measures, including handwashing: the single most important way to prevent the spread of MDRs
- Use of protective clothing
- Appropriate screening of patient for infection, including nasal and rectal swab
- Careful use of antibiotics: antibiogram can be formulated based on routine surveillance of the local organisms and resistance patterns occurring within that particular ICU. From this antibiogram, empiric coverage is possible, taking into account the prior patient's culture data and resistance patterns. Antibiotics should be reviewed every day to determine if they are still needed, need to be altered, or can be stopped based on culture data and the clinical picture.
- Antibiotic stewardship: Oversight of antibiotic prescriptions by ICU pharmacists, ID specialists, and microbiologists may prevent inadequate dosing regimens. This reduction in inappropriate prescriptions then may lead to the reduction of the development of MDR organisms. This also will help to ensure the appropriate adequate antibiotic dosing to avoid underdosing, because this also may lead to the development of MDR organism.
- Culture data: When clinically feasible, sufficient cultures should be sent to facilitate microbiologic identification before the administration of empiric antibiotics.

## CONCLUSION

Infections resulting from MDR organisms continue to be a significant problem, especially in the ICUs, where even infection caused by sensitive organisms already causes additional morbidity, mortality, length of stay, and other hospital costs. Therefore additional efforts are needed to win this battle. Hospitals and other healthcare facilities monitor the spread of MDR organisms and educate caregivers on the best ways to prevent it. Constant evaluation of current practice on the basis of trends in MDR and antibiotic consumption patterns are essential to make progress in this effort.

### Key Points

1. Infection continues to be a major source of morbidity and mortality in the modern intensive care unit (ICU) environment.

2. Multi-drug–resistant organisms continue to represent a significant health threat, especially in the ICU.
3. Hospitals and other healthcare facilities need to monitor the spread of multi-drug–resistant organisms and educate caregivers on the best ways to prevent infection from these organisms.

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