



Mechanisms of Antimicrobial Resistance in Bacteria

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ABSTRACT

The treatment of bacterial infections is increasingly complicated by the ability of bacteria to develop resistance to antimicrobial agents. Antimicrobial agents are often categorized according to their principal mechanism of action. Mechanisms include interference with cell wall synthesis (e.g., β -lactams and glycopeptide agents), inhibition of protein synthesis (macrolides and tetracyclines), interference with nucleic acid synthesis (fluoroquinolones and rifampin), inhibition of a metabolic pathway (trimethoprim-sulfamethoxazole), and disruption of bacterial membrane structure (polymyxins and daptomycin). Bacteria may be intrinsically resistant to ≥ 1 class of antimicrobial agents, or may acquire resistance by de novo mutation or via the acquisition of resistance genes from other organisms. Acquired resistance genes may enable a bacterium to produce enzymes that destroy the antibacterial drug, to express efflux systems that prevent the drug from reaching its intracellular target, to modify the drug's target site, or to produce an alternative metabolic pathway that bypasses the action of the drug. Acquisition of new genetic material by antimicrobial-susceptible bacteria from resistant strains of bacteria may occur through conjugation, transformation, or transduction, with transposons often facilitating the incorporation of the multiple resistance genes into the host's genome or plasmids. Use of antibacterial agents creates selective pressure for the emergence of resistant strains. Herein 3 case histories—one involving *Escherichia coli* resistance to third-generation cephalosporins, another focusing on the emergence of vancomycin-resistant *Staphylococcus aureus*, and a third detailing multidrug resistance in *Pseudomonas aeruginosa*—are reviewed to illustrate the varied ways in which resistant bacteria develop. © 2006 by the Association for Professionals in Infection Control and Epidemiology, Inc. and Elsevier Inc. All rights reserved.

KEYWORDS: Antimicrobial mechanisms of action; Bacterial infections; Microbial mechanisms of resistance; Resistance genes

Throughout history, there has been a continual battle between humans and the multitude of microorganisms that cause infection and disease. Bubonic plague, tuberculosis, malaria, and more recently, the human immunodeficiency virus/acquired immunodeficiency syndrome pandemic, have affected substantial portions of the human population, causing significant morbidity and mortality. Beginning around the middle of the 20th century, major advances in antibacterial drug development and other means of infection control helped turn the tide in favor of humans. With respect to bacterial infections, the

situation dramatically improved when penicillin became available for use in the early 1940s. However, the euphoria over the potential conquest of infectious diseases was short lived. Almost as soon as antibacterial drugs were deployed, bacteria responded by manifesting various forms of resistance. As antimicrobial usage increased, so did the level and complexity of the resistance mechanisms exhibited by bacterial pathogens. The struggle to gain the upper hand against infections continues to this day, although the number of scientists who are developing new antibacterial agents is beginning to dwindle, even as bacteria evolve ever more clever mechanisms of resistance.¹

This article presents a brief overview of the problem of bacterial resistance to antimicrobial agents and examines the mechanisms of action of commonly used antibacterial

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drugs and the mechanisms bacteria have developed to overcome them.

WHY IS RESISTANCE A CONCERN?

There are a number of reasons why bacterial resistance should be a concern for physicians. First, resistant bacteria, particularly staphylococci, enterococci, *Klebsiella pneumoniae*, and *Pseudomonas* spp,²⁻⁷ are becoming commonplace in healthcare institutions. Bacterial resistance often results in treatment failure, which can have serious consequences, especially in critically ill patients. Inadequate empiric antibacterial therapy, defined as the initial use of an antibacterial agent to which the causative pathogen was not susceptible, has been associated with increased mortality rates in patients with bloodstream infections due to resistant *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *K pneumoniae*, *Escherichia coli*, *Enterobacter* spp, coagulase-negative staphylococci, and enterococci.^{8,9} Prolonged therapy with antimicrobial agents, such as vancomycin or linezolid, may also lead to the development of low-level resistance that compromises therapy, but that may not be detected by routine susceptibility testing methods used in hospital laboratories.¹⁰

Resistant bacteria may also spread and become broader infection-control problems, not only within healthcare institutions, but in communities as well. Clinically important bacteria, such as methicillin-resistant *S aureus* (MRSA)^{3,11} and extended-spectrum β -lactamase (ESBL)-producing *E coli*,^{12,13} are increasingly observed in the community. Infected individuals, including children, often lack identifiable risk factors for MRSA, and appear to have acquired their infections in a variety of community settings.^{14,15} Community-associated MRSA strains are typically less resistant to antimicrobial agents than healthcare-associated MRSA, but are more likely to produce toxins, such as Pantone-Valentine leukocidin.¹⁴ The spread of resistant bacteria within the community poses obvious additional problems for infection control, not just in long-term care facilities but also among sport teams, military recruits, and even children attending day care centers—a task that is complicated by the increased mobility of our population. Finally, with respect to the cost-containment pressures of today's healthcare environment, antibacterial drug resistance places an added burden on healthcare costs,¹⁶ although its full economic impact remains to be determined.

HOW DO ANTIBACTERIAL AGENTS WORK?

Most antimicrobial agents used for the treatment of bacterial infections may be categorized according to their principal mechanism of action. There are 4 major modes of action: (1) interference with cell wall synthesis, (2) inhibition of protein synthesis, (3) interference with nucleic acid synthesis, and (4) inhibition of a metabolic pathway (**Table 1**).¹⁷

Antibacterial drugs that work by inhibiting bacterial cell wall synthesis include the β -lactams, such as the penicillins,

cephalosporins, carbapenems, and monobactams, and the glycopeptides, including vancomycin and teicoplanin.^{17,18} β -Lactam agents inhibit synthesis of the bacterial cell wall by interfering with the enzymes required for the synthesis of the peptidoglycan layer.¹⁸ Vancomycin and teicoplanin also interfere with cell wall synthesis, but do so by binding to the terminal D-alanine residues of the nascent peptidoglycan chain, thereby preventing the cross-linking steps required for stable cell wall synthesis.¹⁸

Macrolides, aminoglycosides, tetracyclines, chloramphenicol, streptogramins, and oxazolidinones produce their antibacterial effects by inhibiting protein synthesis.^{17,18} Bacterial ribosomes differ in structure from their counterparts in eukaryotic cells. Antibacterial agents take advantage of these differences to selectively inhibit bacterial growth. Macrolides, aminoglycosides, and tetracyclines bind to the 30S subunit of the ribosome, whereas chloramphenicol binds to the 50S subunit.

Fluoroquinolones exert their antibacterial effects by disrupting DNA synthesis and causing lethal double-strand DNA breaks during DNA replication,¹⁹ whereas sulfonamides and trimethoprim (TMP) block the pathway for folic acid synthesis, which ultimately inhibits DNA synthesis.^{20,21} The common antibacterial drug combination of TMP, a folic acid analogue, plus sulfamethoxazole (SMX) (a sulfonamide) inhibits 2 steps in the enzymatic pathway for bacterial folate synthesis.

Disruption of bacterial membrane structure may be a fifth, although less well characterized, mechanism of action. It is postulated that polymyxins exert their inhibitory effects by increasing bacterial membrane permeability, causing leakage of bacterial contents.²² The cyclic lipopeptide daptomycin apparently inserts its lipid tail into the bacterial cell membrane,²³ causing membrane depolarization and eventual death of the bacterium.

MECHANISMS OF RESISTANCE TO ANTIBACTERIAL AGENTS

Bacteria may manifest resistance to antibacterial drugs through a variety of mechanisms. Some species of bacteria are innately resistant to ≥ 1 class of antimicrobial agents. In such cases, all strains of that bacterial species are likewise resistant to all the members of those antibacterial classes. Of greater concern are cases of acquired resistance, where initially susceptible populations of bacteria become resistant to an antibacterial agent and proliferate and spread under the selective pressure of use of that agent. Several mechanisms of antimicrobial resistance are readily spread to a variety of bacterial genera. First, the organism may acquire genes encoding enzymes, such as β -lactamases, that destroy the antibacterial agent before it can have an effect. Second, bacteria may acquire efflux pumps that extrude the antibacterial agent from the cell before it can reach its target site and exert its effect. Third, bacteria may acquire several genes for a metabolic pathway which ultimately produces altered bacterial cell walls that no longer contain the binding site of the antimicrobial agent, or bacteria may acquire

mutations that limit access of antimicrobial agents to the intracellular target site via downregulation of porin genes.

Thus, normally susceptible populations of bacteria may become resistant to antimicrobial agents through mutation and selection, or by acquiring from other bacteria the genetic information that encodes resistance. The last event may occur through 1 of several genetic mechanisms, including transformation, conjugation, or transduction. Through genetic exchange mechanisms, many bacteria have become resistant to multiple classes of antibacterial agents, and these bacteria with multidrug resistance (defined as resistance to ≥ 3 antibacterial drug classes) have become a cause for serious concern, particularly in hospitals and other healthcare institutions where they tend to occur most commonly.

As noted above, susceptible bacteria can acquire resistance to an antimicrobial agent via new mutations.¹⁸ Such spontaneous mutations may cause resistance by (1) altering the target protein to which the antibacterial agent binds by modifying or eliminating the binding site (e.g., change in penicillin-binding protein 2b in pneumococci, which results in penicillin resistance), (2) upregulating the production of enzymes that inactivate the antimicrobial agent (e.g., erythromycin ribosomal methylase in staphylococci), (3) downregulating or altering an outer membrane protein channel that the drug requires for cell entry (e.g., OmpF in *E coli*), or (4) upregulating pumps that expel the drug from the cell (efflux of fluoroquinolones in *S aureus*).¹⁸ In all of these cases, strains of bacteria carrying resistance-conferring mutations are selected by antimicrobial use, which kills the susceptible strains but allows the newly resistant strains to survive and grow. Acquired resistance that develops due to chromosomal mutation and selection is termed *vertical evolution*.

Bacteria also develop resistance through the acquisition of new genetic material from other resistant organisms. This is termed *horizontal evolution*, and may occur between strains of the same species or between different bacterial species or genera. Mechanisms of genetic exchange include conjugation, transduction, and transformation.¹⁸ For each of these processes, transposons may facilitate the transfer and incorporation of the acquired resistance genes into the host's genome or into plasmids. During conjugation, a gram-negative bacterium transfers plasmid-containing resistance genes to an adjacent bacterium, often via an elongated proteinaceous structure termed a *pilus*, which joins the 2 organisms. Conjugation among gram-positive bacteria is usually initiated by production of sex pheromones by the mating pair, which facilitate the clumping of donor and recipient organisms, allowing the exchange of DNA. During transduction, resistance genes are transferred from 1 bacterium to another via bacteriophage (bacterial viruses). This is now thought to be a relatively rare event. Finally, transformation, i.e., the process whereby bacteria acquire and incorporate DNA segments from other bacteria that have released their DNA complement into the environment after

Table 1 Mechanisms of action of antibacterial agents

- Interference with cell wall synthesis
 - β -Lactams: penicillins, cephalosporins, carbapenems, monobactams
 - Glycopeptides: vancomycin, teicoplanin
- Protein synthesis inhibition
 - Bind to 50S ribosomal subunit: macrolides, chloramphenicol, clindamycin, quinupristin-dalfopristin, linezolid
 - Bind to 30S ribosomal subunit: aminoglycosides, tetracyclines
 - Bind to bacterial isoleucyl-tRNA synthetase: mupirocin
- Interference with nucleic acid synthesis
 - Inhibit DNA synthesis: fluoroquinolones
 - Inhibit RNA synthesis: rifampin
- Inhibition of metabolic pathway: sulfonamides, folic acid analogues
- Disruption of bacterial membrane structure: polymyxins, daptomycin

tRNA = transfer RNA.

cell lysis, can move resistance genes into previously susceptible strains.

Mutation and selection, together with the mechanisms of genetic exchange, enable many bacterial species to adapt quickly to the introduction of antibacterial agents into their environment. Although a single mutation in a key bacterial gene may only slightly reduce the susceptibility of the host bacteria to that antibacterial agent, it may be just enough to allow its initial survival until it acquires additional mutations or additional genetic information resulting in full-fledged resistance to the antibacterial agent.¹⁸ However, in rare cases, a single mutation may be sufficient to confer high-level, clinically significant resistance upon an organism (e.g., high-level rifampin resistance in *S aureus* or high-level fluoroquinolone resistance in *Campylobacter jejuni*). The following case studies, which involve 3 different bacterial species, serve to illustrate several of the ways in which bacteria develop resistance to antibacterial drugs and how different resistance mechanisms may interact to increase the level or spectrum of resistance of an organism. Resistance patterns associated with these bacterial pathogens are discussed in greater detail in other articles in this supplement.

CASE STUDIES

E coli: Development of Resistance to Third-Generation Cephalosporins

E coli is a common cause of urinary tract infections and bacteremia in humans, and is frequently resistant to aminopenicillins, such as amoxicillin or ampicillin, and narrow-spectrum cephalosporins.²⁴⁻²⁶ Resistance is typically mediated by the acquisition of plasmid-encoded β -lactamases, such as TEM-1, TEM-2, or SHV-1, which hydrolyze and inactivate these drugs.²⁷ Some *E coli* strains develop resis-

tance to third-generation cephalosporins and monobactams (i.e., aztreonam) through the acquisition of ESBLs,^{27,28} commonly arising through mutation of TEM-, SHV-, or CTX-M-type enzymes. The ESBLs are not active against cephamycins, such as ceftiofur and ceftiofur²⁷⁻³⁰; however, resistance to cephamycins and other β -lactams may arise as a result of changes in the porins in the outer membrane (proteins that form the water-filled channels through which drugs and other molecules enter the bacterial cell). Such changes decrease or eliminate the flow of small hydrophilic molecules like β -lactam drugs across the membrane.³¹⁻³⁵ The following case illustrates the interaction of these mechanisms of resistance. A 4-year-old girl was admitted to an urban hospital in Atlanta with aplastic anemia and bacteremia. Blood cultures collected during her first week in the hospital were positive with *E coli* isolates that were resistant to ampicillin and narrow-spectrum cephalosporins but remained susceptible to third-generation cephalosporins. Over the next 3 weeks, the child received a variety of antimicrobial agents directed against *E coli* and other suspected bacterial pathogens in an attempt to treat her persistent fevers and bacteremia. The antibacterial agents included penicillins (ticarcillin, oxacillin, and mezlocillin), aminoglycosides (gentamicin), third-generation cephalosporins (cefotaxime and ceftazidime), vancomycin, and clindamycin. During the fourth week of hospitalization, several *E coli* isolates showing increasing resistance to third-generation cephalosporins were recovered from blood cultures. Decreased susceptibility to aztreonam was also observed. The first resistant isolate showed only a modest increase in the minimum inhibitory concentration (MIC) of ceftazidime and other cephalosporins, but subsequent *E coli* isolates showed much higher cephalosporin MICs, particularly to ceftazidime.

Although it is possible that multiple strains of *E coli* were present in this patient's bloodstream, thus accounting for the change in antimicrobial susceptibility patterns, bacterial strain typing studies indicated that there was only a single strain of *E coli* present. This suggested that the *E coli* isolates had acquired a new resistance mechanism during the course of the infection. The β -lactamases present in the bacterial isolates (which were identified using a protein separation technique known as *isoelectric focusing*) indicated that all the *E coli* isolates contained a TEM-1 β -lactamase (isoelectric point 5.4) (Figure 1), whereas the first isolate with low-level ceftazidime resistance contained, in addition, a new β -lactamase, SHV-1, which was produced in large quantities. The β -lactamase studies also indicated that high-level ceftazidime resistance was associated with a mutated form of SHV-1 (which was designated SHV-8), with a broader spectrum of resistance. (The change in a single amino acid, from aspartate to asparagine, at position 178, as documented by DNA sequence analysis of the resistance gene, was responsible for the increased resistance level).³⁰ Polymerase chain reaction assays, designed to detect various β -lactamase resistance genes, confirmed that

the gene encoding the TEM-1 β -lactamase was present in all of the isolates, including those that were initially susceptible to third-generation cephalosporins, and indicated the presence of a second β -lactamase gene (the SHV type) in isolates that were resistant to third-generation cephalosporins (data not shown).

An additional surprise that merited further investigation was the fact that several of the *E coli* isolates also exhibited resistance to cephamycins (i.e., ceftiofur and ceftiofur) in addition to the third-generation cephalosporins. Because ESBLs, like SHV-8, do not mediate resistance to cephamycins, this suggested that the *E coli* isolates had acquired an additional resistance mechanism, beyond the β -lactamases, that was responsible for the cephamycin resistance. Analyses of the outer membrane protein profiles of the ceftiofur-resistant *E coli* isolates indicated loss of the major porin channel (OmpF) in the *E coli* outer membrane through which cephamycins enter the cell (Figure 2). Thus, during a period of <2 months in the bloodstream of the 4-year old patient, an *E coli* strain acquired a new β -lactamase gene that mediated resistance to third-generation cephalosporins (SHV-1), mutated the gene to increase the level of cephalosporin resistance (SHV-8), and downregulated its cell wall porins (OmpF) to increase resistance not only to cephalosporins but cephamycins as well.

***S Aureus*: Development of High-Level Vancomycin Resistance**

MRSA is a common cause of infection among hospitalized patients. Vancomycin is the typical treatment for these infections, but over the last decade there has been increasing concern about the development of MRSA strains with reduced susceptibility to vancomycin. The first report of an MRSA strain with reduced susceptibility to vancomycin (MIC = 8 μ g/mL, reported as a vancomycin-intermediate *S aureus* [VISA]) appeared in Japan in 1997³⁶; this was followed by ≥ 13 confirmed VISA cases in the United States³⁷ (Centers for Disease Control and Prevention [CDC], unpublished observations, 2005). The exact mechanism by which VISA isolates become resistant to vancomycin remains unclear, but it probably involves thickening of the organism's cell wall due to the accumulation of cell wall fragments capable of binding vancomycin extracellularly, and changes in several metabolic pathways that slow cell growth.^{38,39} This was not the mechanism of vancomycin resistance many researchers had predicted, which was the acquisition of the *vanA* vancomycin resistance gene from enterococci. Noble and coworkers⁴⁰ demonstrated that transfer of the *vanA* resistance gene from *Enterococcus faecalis* to *S aureus* was feasible in an in vitro model and on the skin of a mouse. Indeed, it was this transfer of *vanA* in nature, leading to emergence of a highly vancomycin resistant *S aureus* (VRSA) strain (with MICs likely to be >256 μ g/mL), that caused concern among clinicians, microbiologists, and public health officials. Those fears became a reality with the

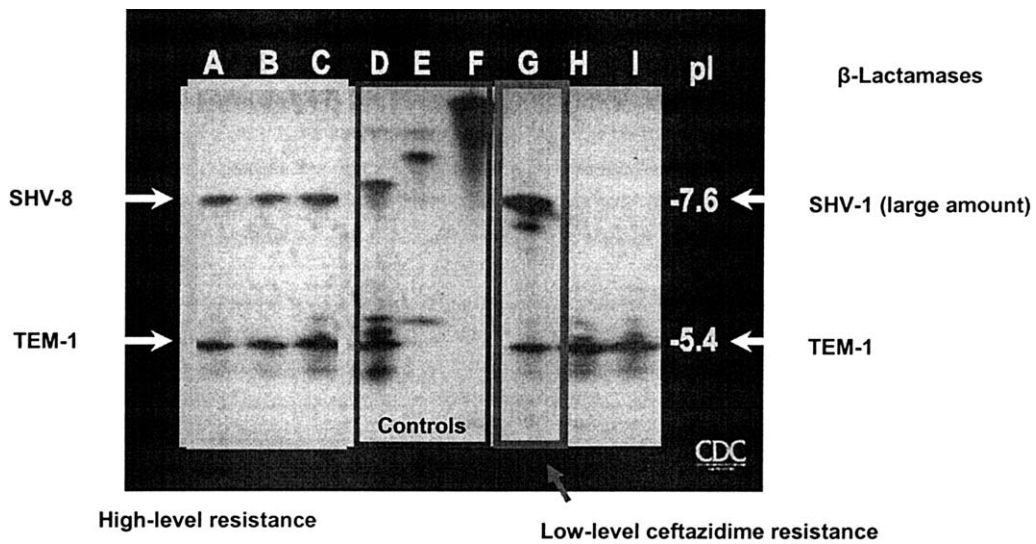


Figure 1 Isoelectric focusing for β -lactamases. The β -lactamases present in the bacterial isolates indicate that all the *Escherichia coli* isolates contain a TEM-1 β -lactamase (isoelectric point 5.4) (lanes A–C and G–I), whereas the first isolate with low-level ceftazidime resistance also contains SHV-1, a new β -lactamase that was produced in large quantities (lane G). High-level ceftazidime resistance is associated with a mutated form of SHV-1, with a broader spectrum of resistance (designated SHV-8) (lanes A–C).

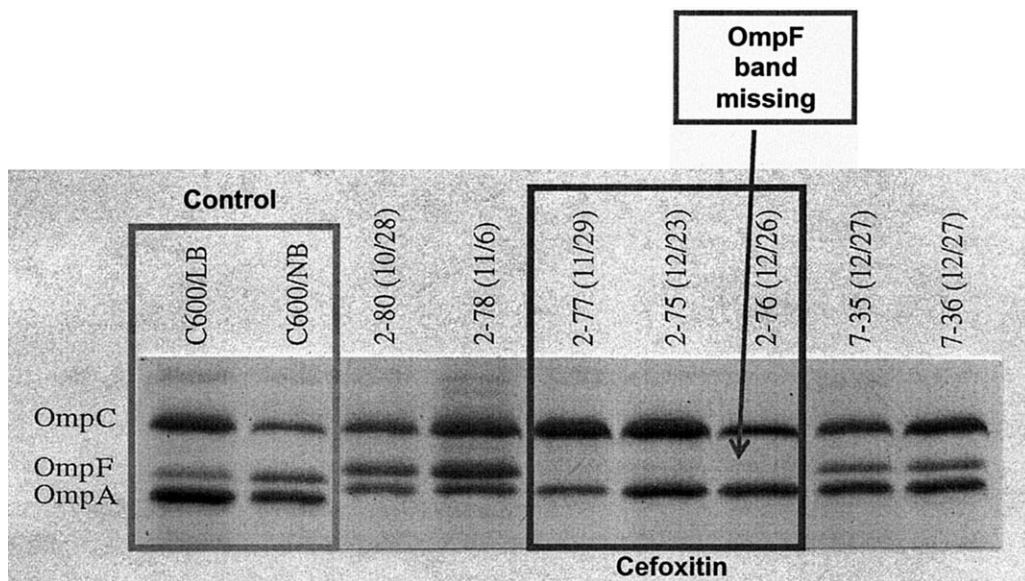


Figure 2 Porin profiles of *Escherichia coli* isolates. Cefoxitin-resistant strains are missing OmpF porin; OmpF is the channel through which cephamycins and other cephalosporins enter the cell.

first reported case of VRSA in the United States in July 2002.^{41,42}

The first case of VRSA involved a 40-year-old woman from Michigan who was undergoing dialysis. The patient had diabetes mellitus, hypertension, peripheral vascular disease, and chronic renal failure.⁴² She developed chronic foot ulcers that eventually became infected with MRSA. Recurrent infections of the foot ulcers led to amputation of the right first metatarsal in February 2002 and the fourth metatarsal in April 2002. During the last hospitalization, the patient developed MRSA bacteremia and an abscess associated with a graft for dialysis access. The patient underwent a number of catheterizations during this time and received a

total of 6.5 weeks of vancomycin therapy over a 6-month period. In mid June 2002, cultures of exudates from the catheter exit site and the catheter tip specimen grew both VRSA and vancomycin-resistant *E faecalis* (VRE). Heel cultures also became positive with VRSA. **Table 2** shows the susceptibility pattern for the VRSA isolated from the exit-site wound.⁴² The VRSA exhibited high-level resistance to vancomycin (MIC = 1,024 μ g/mL) and various other antibacterial agents, but remained susceptible to quinupristin-dalfopristin, TMP-SMX, and linezolid.

The recovery of MRSA and VRE at the infection site suggested that transfer of a *vanA* vancomycin resistance gene from VRE to MRSA had occurred, most likely by

conjugal transfer of plasmid DNA, giving rise to the VRSA. Genetic analysis of the VRSA isolate revealed a multiresistant conjugative plasmid into which the transposon Tn1546, containing *vanA* resistance determinant, had integrated.⁴³ Other genes conferring resistance to TMP, β -lactams, and aminoglycosides were also identified in the plasmid, but these were also present on similar plasmids in the preceding MRSA strain. Thus, it appeared that a preexisting plasmid in the MRSA received the *vanA* transposon from the VRE present in the same infection site, and the selective pressure provided by extended treatment with high levels of vancomycin for MRSA bacteremia selected for the *vanA*-containing MRSA, or more precisely, VRSA.

This case points to the operation of 2 mechanisms of resistance, both involving alteration of target sites in the cell wall of *S aureus*. First, resistance to oxacillin or methicillin is associated with acquisition of a mobile genetic element called SCCmec, which contains the *mecA* resistance gene.⁴⁴ The *mecA* determinant encodes PBP2a, a new penicillin-binding protein with decreased affinity for oxacillin and most other β -lactam drugs. High-level vancomycin resistance occurred because of expression of *vanA*, which is associated with alteration of the vancomycin-binding site in the cell wall.^{45,46} Vancomycin interferes with bacterial wall synthesis by binding with the terminal D-alanine-D-alanine residues of the growing peptidoglycan chain. Expression of *vanA* and other genes on Tn1546 changes the dipeptide terminus from D-alanine-D-alanine to D-alanine-D-lactate, and the affinity of vancomycin for the new terminus is 1,000 times lower than for the native peptidoglycan precursor. Thus, the acquisition of 2 resistance genes, each of which remodel staphylococcal cell walls in a unique way, ultimately resulted in an *S aureus* strain that was highly resistant to both oxacillin and vancomycin.

***P aeruginosa*: Development of Multidrug Resistance**

P aeruginosa is a major cause of opportunistic infections among immunocompromised individuals. The spread of this organism in healthcare settings is often difficult to control due to the presence of multiple intrinsic and acquired mechanisms of antimicrobial resistance. Multidrug resistance is increasingly observed in clinical isolates of *P aeruginosa* collected in the United States.⁴⁷ **Table 3** illustrates a typical susceptibility profile of a multidrug-resistant *P aeruginosa*. This is the type of antimicrobial susceptibility pattern that clinicians dread; unfortunately, it is becoming increasingly common. This *P aeruginosa* isolate was obtained from a patient who sustained burns over 40% of his body during a house fire. He developed his *P aeruginosa* infection after 3 days in the hospital's burn unit. The isolate demonstrated high-level resistance to piperacillin, ceftazidime, cefotaxime, ciprofloxacin, gentamicin, and tobramycin. The patient was treated with a combination of amikacin and imipenem, but subsequently developed sepsis with *P aeruginosa* and *S aureus* and died.

Multidrug resistance often reflects not one but a combination of resistance mechanisms. Efflux pumps are common components of multidrug-resistant *P aeruginosa* isolates, and prevent accumulation of antibacterial drugs within the bacterium, extruding the drugs from the cell before they have the opportunity to achieve an adequate concentration at the site of action. The efflux pumps often work together with the limited permeability of the *P aeruginosa* outer membrane to produce resistance to β -lactams, fluoroquinolones, tetracycline, chloramphenicol, macrolides, TMP, and aminoglycosides.^{48,49} The multidrug efflux systems of *P aeruginosa* are composed of 3 proteins that are structurally and functionally joined. *P aeruginosa* and other gram-negative bacteria possess both an outer membrane and a cytoplasmic membrane, which flank the periplasmic space. The tripartite efflux system is required for effective removal of compounds across both membranes of the cell. The 3 components of the efflux system include an energy-dependent pump located in the cytoplasmic membrane (e.g., MexB), an outer membrane porin (e.g., OprM), and a protein joining them (e.g., MexA).

The 4 major efflux systems of *P aeruginosa* are MexAB-OprM, MexXY-OprM, MexCD-OprJ, and MexEF-OprN.^{48,49} MexAB-OprM and MexXY-OprM contribute to intrinsic multidrug resistance, whereas overexpression of MexXY-OprM or MexCD-OprJ has been associated with acquired multidrug resistance. MexAB-OprM and MexXY-OprM may also be overexpressed. In each case, overexpression is caused by a mutation in 1 of the genes encoding a protein regulating expression of efflux system components. The fact that the efflux systems can mediate resistance to a variety of drug classes makes them very effective mechanisms of resistance.

SUMMARY

It is clear that bacteria will continue to develop resistance to currently available antibacterial drugs by either new mutations or the exchange of genetic information, that is, putting old resistance genes into new hosts. In many healthcare facilities around the world, bacterial pathogens that express multiple resistance mechanisms are becoming the norm, complicating treatment and increasing both human morbidity and financial costs. Prudent use of antibacterial drugs—using the appropriate drug at the appropriate dosage and for the appropriate duration—is one important means of reducing the selective pressure that helps resistant organisms emerge. The other vital aspect of controlling the spread of multidrug-resistant organisms is providing sufficient personnel and resources for infection control in all healthcare facilities. New antibacterial agents with different mechanisms of action are also needed. It is difficult to outsmart organisms that have had several billion years to learn how to adapt to hostile environments, such as those containing antimicrobial agents. Yet, with sufficient efforts to use antimicrobial agents wisely, thereby preventing the emergence of resistant organisms, and strict attention to infection con-

Table 2 Susceptibility pattern for Michigan vancomycin-resistant *Staphylococcus aureus* (VRSA)

| | VRSA MIC ($\mu\text{g/mL}$) | Typical <i>S aureus</i> MIC |
|-------------------------------|----------------------------------|--------------------------------|
| Vancomycin* | 1024 (R) | 1 |
| Oxacillin [†] | >128 (R) | 0.5 |
| Gentamicin [†] | >64 (R) | 4 |
| Rifampin [†] | >8 (R) | 0.1 |
| Levofloxacin [†] | 16 (R) | 0.1 |
| Quinupristin-dalfopristin | ≤ 1 | ≤ 1 |
| Trimethoprim-sulfamethoxazole | 2 | 2 |
| Linezolid | 2 | 2 |

MIC = minimum inhibitory concentration; R = resistant.

*Resistance encoded by *vanA* resistance gene.

[†]Methicillin-resistant *Staphylococcus aureus* recipient strain was already resistant to these drugs.

Adapted from *N Engl J Med*.⁴²

Table 3 *Pseudomonas aeruginosa* susceptibility test report

| Drug | MIC ($\mu\text{g/mL}$) | Interpretation |
|---------------|--------------------------|----------------|
| Piperacillin | >128 | Resistant |
| Ceftazidime | >32 | Resistant |
| Cefotaxime | >32 | Resistant |
| Ciprofloxacin | >4 | Resistant |
| Gentamicin | >16 | Resistant |
| Tobramycin | >16 | Resistant |

MIC = minimum inhibitory concentration.

trol guidelines to contain the spread of resistant organisms when they develop, we should be able to stay at least 1 step ahead of the next resistant plague.

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