Antimicrobial resistance patterns in bacteria, fungi, and viruses are approaching a crisis level in health care today. The Centers for Disease Control and Prevention estimates that approximately 2 million people in the United States are infected with resistant bacteria each year, resulting in at least 23,000 deaths yearly. Infectious disease experts are concerned that up to 50% of antibiotic use in humans and most of the use in animals are inappropriate and unnecessary. Major campaigns to manage this emergency are being implemented. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America developed guidelines for antibiotic stewardship in 2007, which promote the proper use of antibiotic drugs, with continual modification of regimens based on susceptibility reports, patient response, and clinical course.

Most institutions nationwide are continuing to implement these suggestions as well as stringent infection-control protocols to impede the propagation of antimicrobial resistance patterns in their organizations. Experts promote implementing these interventions because “resistance is relentless and unavoidable as long as we use antibiotics.” Drug-resistant strains are emerging, including strains that are pan-resistant. The existing antibiotic repertoire is useless in combating these pan-resistant strains. Confounding this issue is that the antimicrobial drug development process over the next decade is projected to be very limited, which is partially related to lack of a major monetary advantage for pharmaceutical companies to develop antibiotics over medications that warrant lifelong consumption. These developments have led the scientific world to think outside the box and investigate novel interventions to treat or prevent the emergence of resistant organisms. This article explores the concept of antibiotic/antimicrobial resistance.
its evolution, and the emergence of various nonpharmacological strategies.

**Mechanisms of Bacterial Resistance**

When penicillin was discovered and prescribed in the 1940s, researchers documented initial resistance patterns only a few years later, which is an example of **selective pressure**, which refers to antibiotic drugs that will kill susceptible bacteria but allow antibiotic-resistant bacteria to survive. However, this phenomenon was not new. Resistance is an ancient phenomenon. This theory was documented by D’Costa and colleagues, who tested 30,000-year-old permafrost sediments from an archeological site in the Yukon. They found that this ancient soil sample had a collection of genetic material from microorganisms that were resistant to β-lactam, tetracycline, and glycopeptide antibiotics as well as having complete vancomycin resistance. How can those 30,000-year-old microorganisms be resistant to these drugs when they did not exist?

Resistance is not only ancient but also an expected process in nature. Bacteria and other microbes have existed for thousands of years, because the fittest survive. Bacteria become resistant to antibiotics using 4 mechanisms: (1) target modification, (2) efflux, (3) immunity and bypass, and (4) enzyme-catalyzed destruction. If the target of the antibiotic is the bacteria cell wall, bacteria will change the structure of the wall, thereby becoming resistant to that medication. Some bacteria will make their efflux pumps more efficient and are able to pump more antibiotics out of the cell. Some bacteria produce proteins that bind to the antibiotic and prevent it from binding on sites in the bacteria. Bacterial enzyme systems also can alter the structure of antibiotics, thereby eliminating the functional characteristics of the drug.

The majority of nonpathogenic free-living bacteria in the soil are multidrug resistant because they are continuously exposed to bioactive molecules that can activate one of the aforementioned protective mechanisms and produce resistance as the bacteria replicate. The clones of bacteria have genes that are altered as a protective mechanism. These environmental bacteria coexist with pathogenic bacteria in the soil and serve as a reservoir of resistant genetic material, which can be transferred “horizontally” to the pathogens that can instantly acquire resistant genetic material. A common mechanism for horizontal transfer of genetic material is the plasmid. A plasmid is a double-stranded circular or linear DNA molecule that is located outside the chromosomes of the bacteria (extrachromosomal) and allows more mobility of these molecules. Plasmids have been part of the historical evolution of bacteria. Through the conjugation process, the plasmid is transferred from the donor to recipient cell through contact between these cells. If the plasmid contains antibiotic-resistant genetic material, this material will then be integrated into the recipient cell’s genetic framework instead of the dissemination of genetic information through replication.

Limiting the exposure of bacteria to antibiotic drugs would seem to be a logical step in slowing these adaptive processes. However, exposure to antibiotic drugs occurs outside the health care environment and can be contributing to the resistance process. Farm animals are exposed to antibiotics on a regular basis. The agricultural industry is one of the largest consumers of antibiotics, which are used to promote growth and prevent and treat livestock diseases. Antibiotic use for growth promotion is debated by experts, but prevention of diseases in livestock is important for the protection of the consumer. However, treatment of low-grade bacterial infections is considered prophylactic therapy in which the bacteria may be exposed to subtherapeutic dosing. Although these doses do not necessarily kill the pathogen, they may exert pressure, inducing rearrangement of its genetic framework and development of de novo resistance to the antibiotic drugs used. This genetic material can then be transmitted through animal feces to other animals or even humans via the food chain. This use of agricultural antibiotics may be enabling the natural processes soil bacteria use to survive. The European Union has recognized this issue and has implemented steps to limit the subtherapeutic use of antibiotics in food animals. Other countries are following this model to heighten public awareness of these questionable uses of antibiotics. The more we learn about how bacteria have survived for millions of years, the better the insight into solutions for resistance.

**Bacteriophages**

Bacteria have natural enemies, including bacteriophages, which are viruses that infect bacteria. These microbes were initially described in 1896.
as an unidentified substance that can bypass bacterial filter defenses. They were mass-produced for phage therapy in the 1940s. Bacteriophages attach onto a bacterium and inject phage DNA into the cell wall, which promotes lysis of the bacterial cell content and creates a path for escape. The phages replicate faster than the host cell and will produce progeny phages that are released when the host cell ruptures that go on to infect neighboring bacteria. This process can take 30 to 40 minutes. One variety, referred to as lysogenic phages, will invade the DNA structure of the host cell, remain dormant, and replicate with the host cell DNA. They are genetically engineered to reverse the pathogen’s genetic reorganization, the pathogen is reprogrammed to be sensitive to antibiotics again. Bacteriophages are referred to by some as “living drugs.”

The advantage of phage therapy is that it is very specific to a pathogen and it will have minimal impact on the surrounding flora. It also has the unique characteristic of “auto-dosing” and does not depend on specific dosing to be effective. However, the challenge is to determine a virus that is effective against a particular pathogen, which requires the time-consuming identification process of the pathogen. Another concern is that the host cells will eventually be able to acquire immunity against the phages. Some lytic phages can cause rapid destruction, releasing large amounts of endotoxins, resulting in a massive inflammatory response. Phage therapy was used for human therapy in the Soviet Union and is still used in Eastern Europe, especially Georgia. However, clinicians need to understand that this therapy is still in the early developmental stages. New technologies have allowed more methods of genetic engineering, which may improve the safety of phage therapy. Just as in the development of a new drug, phage therapy has many regulatory challenges, which has led the Food and Drug Administration to play a more prominent role. Several recent trials have been conducted in the United States, testing the efficacy of phage therapy in treating leg ulcers and ear infections, which have demonstrated some success, suggesting that phage therapy may play a role in containing antimicrobial resistance in the future.

Bacteriocins
Another mechanism for self-preservation used by bacteria is the development of bacteriocins, which are small ribosomal peptides secreted by many varieties of bacteria to destroy competitive bacteria. These peptides insert themselves into the plasma membrane of bacteria, forming pores, which leads to lysis of the cell. These substances also are thought to be able to interrupt cell wall synthesis and may be able to de-energize the membrane, leading to cell death. Every bacterium is able to produce at least 1 bacteriocin. These peptides are more effective against gram-positive bacteria, because gram-negative bacteria possess a complex outer membrane. This gram-negative outer membrane is composed of lipopolysaccharides, peptidoglycan layers, and other proteins, and has multiple porins that are arranged in varying patterns, making it more protective and challenging to penetrate. Bacteriocins were discovered in 1925 and are currently used in food safety preservation methods. Lactic acid bacteria produce the bacteriocin nisin A, which has been used as a food preservative for many years. This bacteriocin, its numerous variants, and other peptides are being studied to further explore their anti-infective properties especially against multidrug-resistant strains of staphylococci and enterococci.

The advantage of using bacteriocins is that their activity is very specific against one bacterium so the effect on other bacteria is limited. This activity can be directed against pathogens while commensal (beneficial) bacteria will not be compromised. Bacteriocins also are easily degraded by proteolytic enzymes, so lasting effects are not a concern. However, their positive effect is not as long-lasting as antibiotic activity. As with any prolonged exposure, resistance can evolve as a result of the development of immune genetic material. Probiotics are an indirect application of bacteriocins. Probiotic bacteria produce bacteriocins that eliminate pathogenic microbes. More recent scientific investigation into the use of bacteriocins in the treatment of human infection has focused on use against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci infections of the respiratory and gastrointestinal tracts as well as skin infections. Scientists are searching for bacteriocins to use against pathogens such as Listeria monocytogenes and newer resistant strains of Salmonella. Increased interest in this area of inquiry has resulted in the development of a website that provides a current listing of bacteriocins with their associated research.
Fecal Microbiota Transplantation

The term microbiota describes a grouping of commensals, symbiotic, and pathogenic microorganisms whose roles are to maintain a precarious balance in an environment. The gut microbiota (formerly referred to as gut flora) is defined as $10^{10}$ to $10^{12}$ bacterial cells per gram of gut contents, which consists of many different types of organisms that play a major role in the health of the body. The bacteria are divided into 7 genera: Firmicutes, Bacteroidetes, Proteobacteria, Fibrobacter, Verrucomicrobia, Cyanobacteria, and Actinobacteria. Good, or commensal, bacteria in the gut will protect against invading pathogens by competing for nutrition and adhesion sites. This process is referred to as colonization resistance. The use of antibiotics (oral or intravenous) can easily disrupt this balance and cause pathogen activity to predominate, which is evident in today’s health care environment in which nearly a half million people suffer from Clostridium difficile infection (CDI) each year. Although antimicrobials, including vancomycin and metronidazole, are used to treat CDI, this type of infection can reoccur and has become challenging to treat successfully. One of the more promising interventions for treating this infection is replacement of fecal material from a pathogen-free healthy donor to repopulate the gut microbiota. This technique is known as fecal microbiota transplantation (FMT) but also is referred to as fecal transplant therapy. The exact mechanism of this intervention is not completely understood but has demonstrated success in the treatment of CDI. Several types of intestinal bacteria, including Bacteroides spp, are thought to produce bacteriocins that will destroy pathogenic bacteria.

Although this intervention seems unconventional, the theory of fecal transplantation actually has ancient roots. It was used in China for treatment of intestinal disease more than 2000 years ago. The technique for fecal replacement has evolved over the years. The first FMT recorded in the literature was in 1958, when 4 patients were treated for pseudomembranous colitis, which was CDI but had not yet been identified at that time. Current methods for FMT start with emulsifying stool from a pathogen-free healthy donor in a dedicated blender with preservative-free saline. The stool emulsion is administered through an endoscope or a nasogastric tube into the upper gastrointestinal tract or into the lower gastrointestinal tract using a colonscope or via enema. Encapsulated powder of dried stool emulsion that can be used for long-term treatment is a newer administration method being explored. An obvious concern about this intervention is to verify that the donor is pathogen free. Testing for pathogens has become more sophisticated with the use of polymerase chain reactions, and centers that provide this intervention have developed procedures to ensure patient safety. Screening begins with a questionnaire that explores risk factors for possible transmittable diseases. The next phase of screening includes blood testing for various viral, parasitic, and bacterial infections. A final questionnaire is administered the day before donation to make sure the most recent activities and exposures of the donor are captured. The most common indication for the use of FMT has been recurrent CDI, which has been treated with some success. Fecal microbiota transplantation is also being tested with other diseases, including irritable bowel syndrome, ulcerative colitis, some autoimmune diseases, and other disorders, that are associated with change in bowel flora. Colonization resistance is a protective mechanism of the body that involves the balance of the interaction of the immune system and the fecal microbiota to preserve intestinal homeostasis. Research on FMT has revealed more information about fecal microbiota activity and also has served as a stimulus for additional investigation about its use to combat antimicrobial resistance. A recent case study was presented at the Infectious Diseases Society of America conference in 2014, in which FMT was used to clear fecal colonization of carbapenem-resistant enterobacteriaceae. Evidence to support FMT use has been limited because of the lack of randomized controlled trials, which are currently under way. The Food and Drug Administration is starting to play a role in monitoring this intervention, which may be helpful in the understanding and reduction of antimicrobial resistance.

Other Nonpharmacological Interventions to Reduce Resistance

As molecular cellular technology advances, we are better able to understand how cells communicate with each other. Originally, it was thought that microbes did not possess this level of communication sophistication, but it was
discovered that microbes do have messenger molecules that create a network between cells for defense. Pathogens rely on cell-to-cell communication mechanisms to synchronize microbial activities essential for infection. This process is referred to as quorum sensing where molecules of 1 microbe signal similar molecules of another microbe.\textsuperscript{11, 23} This cross-talk between microbes occurs through signaling involving cytosolic transcription factor or membrane receptors, which is a stimulus and response mechanism that increases as the population of a microbe increases.\textsuperscript{11, 23} Researchers theorize that if this communication between microbes were disrupted, the ability of the microbe to protect itself against destruction could be altered. This theory is referred to as quorum quenching. Quorum quenching is achieved through mimicking the structure of quorum sensing molecules or inhibition of enzymes involved in the synthesis of quorum sensing molecules.\textsuperscript{11, 23} This disruption of communication between microbes could alter their protective mechanisms against attack, thereby limiting microbial resistance.\textsuperscript{11}

Microbes also have developed the ability to cannibalize each other. Peptides or proteins are released by cells and cause cell lysis of sibling cells. The nutrients from the lysed cells are used for food and spore development of the surviving cells.\textsuperscript{11} These proteins are referred to as killing factors. This activity was best studied in \textit{Bacillus subtilis} and is now being studied as a method to use these killer proteins against methicillin-resistant \textit{Staphylococcus aureus} and \textit{Staphylococcus epidermidis}, which are both opportunistic pathogens.\textsuperscript{11}

Scientists continue to explore interventions to help decrease antimicrobial resistance. Other drugs that are not antibiotics have been found to have some antimicrobial activity. Table 1 includes a list of drugs that may possess this type of activity.\textsuperscript{24} The mechanism of action is not well understood but is thought to be related to alteration of cell permeability.\textsuperscript{11} The problem with this finding is that the antimicrobial activity of these drugs is achieved at a much higher concentration than usual physiological concentrations.\textsuperscript{11, 24} Higher concentrations could produce increased adverse effects and/or toxicity of these drugs and must be balanced with their antimicrobial activity before this intervention can be considered as a safe alternative.

**Summary**

Antimicrobial resistance “threatens to return us to the time when simple infections were often fatal.”\textsuperscript{11} This health care crisis has prompted the White House to release a paper describing a national strategy to combat

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### Table 1: Nonantibiotic Drugs With Possible Antibiotic Activity\textsuperscript{*}

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenergic receptor antagonists</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Mucolytic agents</td>
</tr>
<tr>
<td>Mucolytic agents</td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory agents</td>
<td>Neuroleptics</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>H, antihistamines</td>
</tr>
<tr>
<td>H, antihistamines</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Proton pump inhibitors</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Based on Nigam et al.\textsuperscript{11}

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### Table 2: Summary of Alternatives to Antimicrobials

<table>
<thead>
<tr>
<th>Alternative</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriophages</td>
<td>Specific viruses that destroy a particular microbe</td>
</tr>
<tr>
<td>Bacteriocins</td>
<td>Peptides secreted by various bacteria that will eliminate competitive bacteria</td>
</tr>
<tr>
<td>Fecal microbiota transplantation</td>
<td>Reconstitution of gut microbiota that has been altered by antibiotic use</td>
</tr>
<tr>
<td>Quorum quenching</td>
<td>Disruption of cellular signaling that synchronizes cellular microbial activity</td>
</tr>
<tr>
<td>Killing factors</td>
<td>Peptides released by bacteria to kill sibling cells and use as nutrition during starvation</td>
</tr>
<tr>
<td>Nonantibiotic drugs</td>
<td>Drugs that have antimicrobial activity that may disrupt cell permeability</td>
</tr>
</tbody>
</table>
antibiotic resistance in September 2014. One of the objectives of this national strategy is to:

Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic resistance and the spread of resistance genes that are common to animals and humans.

This objective is asking the scientific community to learn how microbes have successfully survived for thousands of years. Understanding the natural defenses of microbes can help discern how to contain them. This article has provided some of these survival mechanisms (Table 2), but this is only the beginning of this type of research. Many of these survival mechanisms were discovered in the early 19th century or earlier. However, science opted to use antibiotic drugs that were newly developed to treat infections. That option is not as readily available today. New antibiotic drugs are being developed but at a very slow pace, while the microbes continue to develop mechanisms to survive. The nonpharmacological interventions discussed in this article provide additional tactics to combat antimicrobial resistance. However, back-to-basics interventions, including proper hand-washing techniques, observation of isolation techniques, and collegial review of proper procedure techniques as well as hospital epidemiology protocols, must continue. Nursing plays a significant role in ensuring that these basic interventions are properly implemented. Continual review of antibiotic therapy should be a part of the daily multidisciplinary discussion of patient care, so that antibiotic drugs can be discontinued if not needed. Effective antibiotic stewardship is not limited to one discipline but is a combined monitoring effort of all health care disciplines. These core interventions, when combined with the new innovations discussed, may help win the battle against resistant microbes.

REFERENCES


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