Fighting Antimicrobial Resistance with Genetics and Genomics

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The United Nations General Assembly defined antibiotic resistance as not only “the greatest” but also the “most urgent global risk” (Centers for Disease Control and Prevention [CDC], 2018a; Lin, Koskella, & Lin, 2017, p. 163). Some bacterial strains, such as carbapenem-resistant *Klebsiella pneumoniae*, have very few treatment options. Infections with this organism are associated with a 40%-70% mortality rate (Hauck et al., 2016). Furthermore, some bacteria are labeled not only as difficult to treat, but also untreatable with conventional antibiotics (Frieri, Kumar, & Boutin, 2017). There are reports of antimicrobial resistance (AMR) for every approved antibiotic available (Baker, Payne, Rappuoli, & De Gregorio, 2018). Warnings of a return to a pre-antibiotic era are increasing in frequency (Blaskovich, 2018).

Fewer antibiotic options are available not only because bacteria are developing resistance to known therapies, but also because fewer antibiotics are being developed. Bacteria are able to gain rapid resistance, decreasing commercial interest in the development of new antibiotics. For example, from 1983 to 1987, 16 new antibiotics were approved by the U.S. Food and Drug Administration. However, only six new antibiotics were approved from 2010 to 2016 (Boucher et al., 2013; Luepke et al., 2017).

Despite the many persistent challenges of AMR and continued decreased effectiveness of antibiotic treatment options, some novel therapies are on the horizon (Lin et al., 2017; Rappuoli, Bloom, & Black, 2017). Many emerging therapies for bacterial infections are developing as a result of advances in genetics and genomics. Awareness of these therapies is essential for nurses as clinical trials enroll patients, patients read about these therapies in the news and seek information from nurses, and these therapies enter the healthcare setting.

**Phage Therapy**

Bacteriophages (also known as phages) are bacteria-specific viruses that can infect and kill bacterial cells. Phages are non-living entities that inject their DNA or RNA into bacterial cells, using their host to replicate their genetic material (Greene, 2018). A hundred years ago, phages were used to treat Shigella dysenteriae (Cisek, Dąbrowska, Gregorczyk, & Wyżewski, 2017). However, with the discovery of antibiotics, uses of phage therapy fell by the wayside. As researchers...
explore methods of managing AMR, the study of phages is reemerging.

The Eliava Institute has used phage therapy in preclinical and clinical treatment of bacterial infections (Kutateladze, 2015). Phages have been used for prophylaxis and treatment of infections. For example, Fish and colleagues (2016) used phage therapy to treat diabetic foot ulcers unresponsive to antibiotics, leading to successful recovery. Completed phase I/II clinical trials support the safety and efficacy of phage therapy in treating antibiotic-resistant Pseudomonas aeruginosa (Lin et al., 2017; Wright, Hawkins, Ånggård, & Harper, 2009). In vitro and ex vivo models have demonstrated phage therapy combined with antibiotics was more effective than antibiotic therapy alone for treatment of Clostridium difficile (Wang, Euler, Delaune, & Fischetti, 2015).

Potential problems with phage therapy include the specificity of phages. Phages’ specificity to the species and strain of bacteria may be a disadvantage when infections are colonized by multiple bacterial strains (Servick, 2016). Phage therapy then would be only as effective as the knowledge of which pathogens are causing the infection, as opposed to broad-spectrum antibiotics which are effective against a number of bacterial strains. As a result, because phages are extremely bacteria-specific, it is difficult to have phage therapy available ahead of time and ready when needed for treatment. Researchers are exploring creation of readily available phage treatment options based on known bacteria in an environmental reservoir, such as a hospital (Mattila, Ruotsalainen, & Jalasvuori, 2015).

Another promising application of phage therapy is the ability of phages to break down bacterial biofilms. High doses of antibiotics are often required to treat bacterial infections with the presence of biofilms; these high doses can lead to tissue toxicity and the biofilms may return when the course of antibiotics is completed. Use of phage therapy to combat the development of biofilms is clinically significant because it can help eradicate biofilms on areas of prevalence (e.g., catheters, prostheses, implanted medical devices) (Lin et al., 2017).

A very promising application of phage therapy in fighting AMR is genetic technology such as CRISPR/Cas, which allows researchers to alter an organism’s DNA (Caplan, Parent, Shen, & Plunkett, 2015). This technology can be used to bioengineer phage therapy to specifically target resistance genes in bacteria. Genetic sequencing technology currently is used to help researchers identify which bacterial genes are related to the development of antibiotic resistance; the use of technology such as CRISPR/Cas combined with phage therapy could allow researchers to target the specific genes that lead to antibiotic resistance (Lin et al., 2017).

Convergent Evolution

An additional genetic/genomic tool to fight antibiotic resistance involves the use of sequencing technology and the study of evolution. Researchers are studying how outside influences can lead to predictable patterns of evolution of bacteria (Marvig, Sommer, Molin, & Johansen, 2015). If these patterns can be predicted, they can be used to develop treatment options against the bacteria. Marvig and colleagues used genome sequencing to study the evolutionary patterns of P. aeruginosa in the lungs of patients with cystic fibrosis. While evolution is often considered as occurring on a long-term timeline, researchers were able to see how bacteria evolved even during the brief course of antibiotic therapy. These authors noted 52 bacterial genes mutated more quickly than expected. This suggested the presence of convergent evolution, meaning genetic variation moved toward a common goal of helping bacteria evolve capabilities for thriving in the lungs of individuals with cystic fibrosis. Examples of such capabilities include biofilm formation, antibiotic resistance, and motility. Researchers further explored genetic changes among bacteria and reported the interactions among genetic variants also could provide insight into which mutations may occur.

Future studies are going to use metagenomic sequencing (the study of genetic samples directly from the environment) to explore how the environment can affect the growth or inhibition of specific bacterial traits (Snitkin & Segre, 2015). The study of convergent evolution can help researchers understand factors that cause bacteria to develop specific mechanisms of resistance. Furthermore, researchers can use this information to explore strategies to prevent resistance from occurring by avoiding factors that promote the formation of resistance, or to be equipped better to fight resistance with knowledge of how certain variables can cause it to occur.

Vaccines and Reverse Vaccinology

Vaccines are some of the most promising tools to address the growing concern of antibiotic resistance. Vaccines can prevent bacterial infection, leading to a decreased need for antibiotic use and thus decreased risk of bacterial resistance (Baker et al., 2018; Rappuoli et al., 2017). Vaccines are available against Streptococcus pneumoniae and Haemophilus influenzae; vaccines against C. difficile, Staphylococcus aureus, and other bacterial infections are in the clinical development phase (Baker et al., 2018).

Reverse vaccinology is an additional tool derived from the ability to sequence the genomes of microorganisms. The term reverse vaccinology is derived from the creation of vaccines using data from genomic information; this information undergoes a computerized analysis to identify antigens that may be candidates for vaccine creation (Baker et al., 2018; Rappuoli, 2000). This is in contrast to traditional
vaccine development that first requires the identification of pathogens that cause diseases, followed often by trial-and-error identification of components that can be used to create vaccines. The Group B meningococcus vaccine was the first successful use of reverse vaccinology (Rappuoli, 2000). Before use of reverse vaccinology, scientists attempted unsuccessfully for 4 decades to develop this vaccine.

Researchers are using reverse vaccinology currently in an attempt to create a universal influenza (fl) vaccine. Traditional flu vaccines have to match circulating viral strains, creating variable vaccine accuracy year to year. A universal flu vaccine would provide long-lasting immunity and be developed from a region in the viral genome that is common to all flu strains. This increases the likelihood of effectiveness against seasonal flu strains and emerging highly pathogenic flu strains such as H5N1 and H7N9 (Rappuoli, Bottomley, D’oro, Finco, & De Gregorio, 2016). Nurses should be aware that many promising applications of reverse vaccinology remain in development and clinical trial stages.

**Nursing Implications**

Although genetics and genomics are leading advances into fighting antibiotic resistance, many nurses never had a genetics course in their undergraduate studies (Seven, Akyüz, Elbüken, Skirton, & Öztürk, 2015). Because the field is advancing, continuing education is an essential resource for nurses to learn about emerging genetic/genomic applications with possible implications for their practice.

While some technologies to combat AMR remain on the horizon, the U.S. Food and Drug Administration approved phase I and II clinical trials of intravenously administered phage therapy in 2019 (Voelker, 2019). In addition, clinical trials for the universal flu vaccine are being conducted (National Institutes of Health, 2019). As promising tools to help combat AMR come closer to clinical availability, nurses will be able to provide patient education based on therapies that are clinically available as well as those still in development phases, and be aware of options that may be beneficial for specific patient populations. Working collaboratively with the interprofessional healthcare team, nurses may identify patients who could benefit from clinical trials if traditional therapies are ineffective. Nurses are often the first providers to recognize a clinical concern because they administer medications, monitor adverse effects, assess patients, and communicate findings to the interprofessional team. They thus may be the first to identify signs of AMR and develop a collaborative plan of care with the interprofessional healthcare team. Keeping current with clinical innovations allows nurses to have comprehensive understanding of key areas of need such as AMR and efforts to address those needs.

Although frequently discussed as a key nursing role, patient education is especially important due to the complexities of genetics/genomics and AMR. The complexities of patient education include discussing topics such as causes of AMR as well as clinical tools to combat it. Information should be provided in a usable, relatable format. Foundational components of patient education include discussing viral vs. bacterial infections, including the fact that antibiotics do not benefit, and may have harmful side effects, for individuals with viral infections. Patients should be taught to take antibiotics as directed, not skip doses of antibiotics, complete an entire course of a prescribed antibiotic, and not take antibiotics prescribed for others (U.S. Food & Drug Administration, 2011). Nurses also should discuss strategies to prevent infection (e.g., handwashing). Those foundational components are applicable for broad discussions of infection prevention and antibiotic use.

Additional, AMR-specific components of patient education include discussing signs and symptoms of continuing infection during and following a course of antibiotics. This is a complex topic because infections may be asymptomatic, and signs and symptoms may be specific to the site of infection (e.g., urinary tract infection) or organism-specific (Fisher, Gollan, & Helaine, 2017; Hawkey et al., 2018). Educating patients about the presence of infection without specific signs and symptoms is important to highlight the need for follow-up visits with the healthcare provider. If a patient completes a course of antibiotics for a urinary tract, respiratory, or skin infection, education should include site-specific signs and symptoms that may indicate continuing infection. For example, mild, lessening dysuria following treatment for a urinary tract infection may be present following successful treatment; however, persistent or worsening dysuria, lower back or flank pain, dark or cloudy urine, fever, presence of chills, or feeling shaky could indicate continuing infection and the patient should contact the healthcare provider. Finally, nurses should be aware of and provide patient education about the signs and symptoms of common AMR bacteria (see Table 1). Nurses also should address sequelae of antibiotic resistance, such as the need for additional provider visits, additional medications and costs, possible medication side effects, and the dangers of antibiotic-resistant organisms (World Health Organization, n.d.).

A frequently debated patient education topic is that of vaccination. While not considered a typical teaching topic related to AMR, vaccination is one of the most important tools to battle antibiotic resistance. Some patients believe vaccines are not safe or too many of them are administered (Hulse & Bland, 2015; Laskowski, 2016). Vaccines have been evaluated repeatedly, every time demonstrating their safety and effectiveness. However, if individuals perceive additional vaccinations as a burden, they are less likely to receive and benefit from them. Nurses can help to battle AMR by discussing the safety of...
### TABLE 1.
Multi-Drug Resistant Bacteria and the Associated Clinical Presentation

<table>
<thead>
<tr>
<th>Infectious Organism</th>
<th>Background</th>
<th>Clinical Presentation</th>
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<tr>
<td>Carbapenem-resistant <em>Enterobacteriaceae</em> (CRE)</td>
<td>Infection can result in mortality rates of up to 50%. CRE is difficult to treat due to high levels of resistance to multiple antibiotics (CDC, 2015).</td>
<td>Older adults, immunosuppressed persons, and those with multiple comorbidities (e.g., diabetes) are most likely to be affected. CRE may cause UTI, pneumonia, and bacteremia, although less frequent skin and soft tissue infections also may occur. Symptoms may not be specific and may be difficult to assess. They may include dysuria, fever, or bacteremia. Removal of lines, catheters, or devices that may be the source of infection should be considered (Perez &amp; Van Duin, 2013).</td>
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<td><em>Klebsiella pneumoniae</em></td>
<td>A multi-drug resistant organism identified as an urgent threat to human health by the WHO and CDC (Kidd et al., 2017)</td>
<td>Previously considered to infect primarily immunocompromised individuals; emergence of new strains has resulted in increased infections among healthy individuals. <em>K. pneumoniae</em> can cause a wide range of illnesses (e.g., UTI, pneumonia, liver abscess, bacteremia). Associated symptoms may include fever, dysuria, abdominal pain, chills, fatigue, nausea/vomiting, and abdominal pain (Kamal, Williams, Akbar, Khan, &amp; Kadaria, 2017; Paczosa &amp; Mecsas, 2016).</td>
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<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td>Bacteremia due to MRSA infection is associated with high rates of mortality and morbidity (Hassoun, Linden, &amp; Friedman, 2017).</td>
<td>MRSA may cause bacteremia, pneumonia, surgical site infections, and skin infections. Signs and symptoms of infection may include erythema, swelling, pain and drainage at the site, and fever. Approximately 5% of patients in U.S. hospitals are colonized with MRSA in the nose or skin (CDC, 2019).</td>
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<td><em>Mycobacterium tuberculosis</em></td>
<td>Treatment of drug resistant tuberculosis (DR-TB) is a notable clinical challenge with few viable solutions. Treatment can extend approximately 2 years and include more toxic, less effective second- or third-line agents (Hoagland, Liu, Lee, &amp; Lee, 2016).</td>
<td>Tuberculosis (TB) often affects the lungs and other parts of the body (e.g., brain, spine, kidneys). DR-TB is spread the same way as TB; DR-TB can develop if an individual does not complete the course of treatment, the medication is not taken regularly, or incorrect dose/length of treatment is prescribed (CDC, 2016b, 2017).</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Complications include ectopic pregnancy, infertility, pelvic inflammatory disease, increased rate of transmission/acquisition of HIV. In 2006, the CDC recommended five treatment options for gonorrhea, currently one option remains: later-generation cephalosporins (CDC, 2018b; Wi et al., 2017).</td>
<td>Signs and symptoms may include pain and burning with urination, genital discharge, or bleeding between menstrual periods. If symptoms persist following treatment, the individual should return to the provider for follow-up evaluation (CDC, 2016a, 2018b).</td>
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<td><em>Streptococcus pneumoniae</em></td>
<td>Major cause of otitis media, pneumonia, meningitis, bacteremia, and sepsis; increased resistance identified to multiple classes of antibiotics (Cherazard et al., 2017)</td>
<td>Signs and symptoms vary based on the area infected. They may include cough, ear pain, shortness of breath, neck stiffness, sensitivity to light, confusion, fever, or chills. Severe infection can cause hearing loss or brain damage (NYU Langone Health, n.d.).</td>
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<tr>
<td>Vancomycin-resistant <em>Enterococci</em> (VRE)</td>
<td>Bacteremia due to VRE is associated with 2.5-fold increase in mortality (Faron, Ledeboer, &amp; Buchan, 2016).</td>
<td>VRE is associated with a variety of illnesses including UTI, endocarditis, intra-abdominal and pelvic infections, skin infections, and bacteremia; may cause central nervous system infections (O’Driscoll &amp; Crank, 2015).</td>
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CDC = Centers for Disease Control and Prevention, DR-TB - drug-resistant tuberculosis, UTI = urinary tract infection, WHO = World Health Organization
Learning about tools such as genetic/genomic advances helps nurses understand how resistance develops and how researchers and clinicians are working collaboratively to combat it. Articles such as this one can be used in nursing practice now and can inform nurses of potential therapies.

REFERENCES


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