Antimicrobial Resistance History and Perspectives

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ABBREVIATIONS

AMR – antimicrobial resistance, antimicrobial-resistant, CDC – Centers for Disease Control and Prevention, HAIs – healthcare-associated infections, MDR – multidrug-resistant, WHO – World Health Organization

INDEX TERMS

antibiotic resistance, antibiotics, antimicrobial resistance, antimicrobial susceptibility testing, resistance mechanisms

Learning Objectives

1. Discuss the history of antibiotics and emergence of resistance
2. Identify current antimicrobial-resistant threats and associated challenges
3. Identify specific issues that must be addressed worldwide

ABSTRACT

The Centers for Disease Control and Prevention (CDC) estimates that over 2 million individuals in the United States are infected by antibiotic-resistant organisms every year, and that these infections cause at least 23,000 deaths.[1] This represents a significant threat to public health and requires immediate action. To effectively combat infections caused by these organisms, several strategies must be employed. Important strategies include understanding microbial mechanisms of pathogenesis and resistance, development of novel antimicrobials and diagnostic tools, and prevention of infections. This series will explore the phenomenon of antimicrobial resistance and the role that healthcare professionals play in identifying and combating these organisms.

History of Antibiotics and Emergence of Resistance

Antibiotics are defined as substances that have bactericidal or bacteriostatic effects. In other words, they are substances that are able to kill or slow the growth of bacteria. Antibiotics conventionally target three broad bacterial functions: cell wall synthesis, DNA replication, and RNA transcription or protein synthesis.[2] Bacteria are not the only microorganisms inhibited by therapeutics. Other microbes, such as viruses and fungi, can be treated using antimicrobial drugs. This series will focus primarily on antibiotics, but readers should be aware that the phenomenon of antimicrobial resistance (AMR) extends beyond bacterial resistance.[3]

The antibacterial properties of molds have been noted in the modern era since at least 1640 when John Parkington, a London apothecary and the King's Herbarion, suggested treating various conditions—including infections—with molds.[4] In 1929, Alexander Fleming published his observations of bacterial inhibition by a "mould broth filtrate" from a *Penicillium* species.[5]

He called this filtrate "penicillin." Over a decade later, the penicillin molecule was purified and its efficacy as an antibacterial therapeutic was tested in animal models.[6] Isolated penicillin was subsequently tested in humans for toxicity[7] and ultimately for effectiveness against infections.[8] The remarkableness of these findings was recognized in 1945 when the Nobel Prize in Medicine was awarded to three scientists—including Fleming—for their work in discovering penicillin and identifying its curative effects.[9] Administration of penicillin as an antibacterial therapeutic became widely available following World War II. The miracle age of antibiotics had begun.

The discovery and application of penicillin to treat infectious diseases heralded a turning point in medical care. Penicillin and the scores of antibiotics identified since 1928 have saved the lives of millions of people worldwide.[10] Prior to the introduction of antibiotics, a period often referred to as the pre-antibiotic era, a minor infection could—and frequently would—become life-threatening. Despite the seemingly miracle-like properties of antibiotics, resistance to these drugs was seen simultaneously with their discovery. In the same publication where he described penicillin's antibiotic properties, Fleming noted that some bacteria were not inhibited by penicillin.[5] In fact prior to the widespread use of penicillin, *Staphylococcus aureus*, which was identified by Fleming as susceptible to this drug, developed penicillin resistance.[1] Since then, introduction of various antibiotics is often quickly followed by resistance to that antibiotic. Compounding this issue is the relative lack of novel antibiotics being introduced [1]. In other words, bacteria are evolving resistance more quickly than we can develop new antibiotics to treat them. Widespread antibiotic resistance coupled with a lack of novel antibiotics led the World Health Organization (WHO) in 2014 to project the imminence of a post-antibiotic era, where once again we would see minor infections become potentially deadly.[11, 12]

An important factor contributing to the emergence of antibiotic resistance is the misuse of antibiotics.[1] This includes over prescription of antibiotics, as well as overuse in the agricultural sector. It has been suggested that up to 50% of antibiotics prescribed for humans are unnecessary.[1] Similarly, use of antibiotics in food animals has been linked to antibiotic-resistant bacteria in humans, and thus represents a threat to human health.[13] Antimicrobial stewardship is therefore often aimed at improving misuse of antibiotics in both healthcare and agriculture.[1]

Current Antimicrobial Threats and Associated Challenges

As an indicator of how serious the issue of antibiotic resistance has become, in 2013 the CDC compiled their first ever threat report detailing the antibiotic-resistant threats in the United States and proposing strategies to address these threats.[1] The report provides information on specific bacteria and one fungus that are emerging as concerning, serious threats, and urgent threats to public health. At the top of the CDC's threat list are three organisms that in 2013 posed an urgent threat to public health: *Clostridium difficile*, recently reclassified as *Clostridioides difficile*;[14] carbapenem-resistant *Enterobacteriaceae* (CRE); and drug-resistant *Neisseria gonorrhoeae*. Since 2013, there has been an increase in resistance to drugs of last resort worldwide in both CRE and *N. gonorrhoeae*.[15-17] The overarching concern with antibiotic-resistant organisms is that there will soon be widespread pan-resistance. The emergence of resistance to drugs of last resort indicates that this is a realistic concern. In fact, pan-resistant *Klebsiella pneumoniae* has already been isolated here in the United States.[17]

Along with representing a significant threat to public health, antimicrobial-resistant infections further present a substantial economic burden in the United States. Per-person cost estimates in the United States for those infected by AMR organisms ranges from $18,588 to

$29,069, and total economic burden estimates in the United States are as high as $20 billion per year in total health care costs.[18] Antimicrobial-resistant infections are also frequently identified as healthcare-associated infections (HAIs) which represent an additional financial burden. The projected global economic impact estimates will be discussed later in this series.

In attempting to track, treat, and prevent infections caused by AMR organisms, understanding how these organisms are transmitted between individuals is important. Several routes of transmission have been identified for AMR organisms. In a healthcare setting, organisms are frequently spread from patient to patient by healthcare-workers hands.[19] Improving compliance with hand hygiene protocols can therefore lead to decreased organism prevalence over time.[20] Medical equipment is also a frequent route of transmission. For example, the 2015 outbreak of carbapenem-resistant *K. pneumoniae* at a UCLA medical center was facilitated by contaminated duodenoscopes.[21] Similarly, various hospital surfaces are also often cited as routes of transmission. Supporting this, a recent study identified hospital drains as a reservoir for antibiotic-resistant bacteria.[22] Identification of transmission routes opens the door for intervention prior to transmission, which can decrease the prevalence of AMR organisms and ultimately prevent disease.[20]

Recognition of how organisms acquire resistance mechanisms is vital to combating the spread of resistance. In bacteria, antibiotic-resistant genes can encode intrinsic resistance in a species, such as *Enterococci* species' intrinsic resistance to cephalosporins[23] or intrinsic resistance to ampicillin within *Klebsiella* species.[24] Bacteria can also acquire resistance to various antibiotics. Plasmid-mediated antibiotic resistance loci are of primary concern among acquired mechanisms of resistance since they are easily transmissible between multiple bacterial species. This means that previously susceptible pathogens can easily become resistant.[25] Of

recent concern is the plasmid-mediated *mcr-1* gene first identified in Gram negative organisms in China,[15] but recently identified in *Escherichia coli* isolated from a human patient in the United States.[26] The *mcr-1* gene is of particular concern since it encodes resistance to colistin, a polymyxin drug of last resort, indicating that easy transmission between multidrug-resistant (MDR) bacteria could lead to pan-resistance. Mechanisms of antibiotic resistance will be discussed in depth later in this series.

Once a patient becomes infected, laboratory testing to identify antimicrobial-resistant organisms and their resistance patterns is an integral part of treatment. Accurate testing and reporting plays an important role in antimicrobial stewardship as well, allowing physicians to administer appropriate antibiotics.[27] As the landscape of resistance continues to evolve, the methods and technologies used to identify organisms and resistance patterns must also evolve.

Series Focus

As microoorganisms continue to evolve novel mechanisms of resistance and exchange mobile genetic elements amongst themselves, we must discover new ways to combat them. This arms race between humanity and antimicrobial-resistant organisms represents a striking example of the Red Queen Hypothesis, which suggests that organisms must continually evolve and adapt amidst the pressures of other organisms' continuous evolution in order to simply maintain the status quo.[28] Essentially, we are running as fast as can in order to stay in the exact same place. Ultimately our goal is to eventually outrun and outfight these microorganisms. To that end, the CDC has proposed four Core Actions to help combat antibiotic resistance here in the United States: 1) prevention of both infections and the spread of antimicrobial resistance; 2) tracking resistance patterns, both domestically and globally; 3) improving antibiotic stewardship; and 4)

development of new antibiotics and novel diagnostic tests.[1] The articles in this series will discuss various aspects of several of these Core Actions and how they contribute to understanding and combating infections caused by AMR organisms. This series seeks to provide readers with a broad understanding of the tools and methods currently in place to fight these infections as well as an introduction to development of new tools and methods. Readers will also receive an overview of challenges frequently encountered in this "War Against Bugs." Before we can effectively combat AMR organisms, we must understand how they are able to evade current therapies. Knowledge of both the mechanisms of antimicrobial therapies and mechanisms of resistance employed by organisms are vital to this understanding. Furthermore, as resistance spreads, development of novel antimicrobials is necessary. These issues will be discussed in the second article of this series, *Antibiotics and Bacterial Mechanisms of Resistance*. Accurate antimicrobial susceptibility testing is imperative for effective treatment of infections and reflects the importance of the role of the clinical microbiology team in combating AMR organisms. Current antimicrobial susceptibility testing methods and challenges, as well as the future of testing, is addressed in the third article, *Antimicrobial Susceptibility Testing Paradigms: Current Status and Future Directions.* Finally, it is important to remember that antimicrobial resistance is a global problem and therefore requires a global solution. Successful reduction in the spread of resistance involves the efforts of scientists, physicians, the agricultural sector, politicians, and regulatory agencies worldwide. Multiple issues have contributed to the emergence of antimicrobial resistance, suggesting that a multifaceted approach will be required to combat AMR organisms. Antimicrobial resistance as a global, multi-layered issue will be discussed further in the final article of this series, *Globalization and Antimicrobial Resistance: A Moving Target*.

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