Overview: Global and Local Impact of Antibiotic Resistance

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KEYWORDS

• Antibiotic resistance • Infections • Agriculture • Public health

KEY POINTS

- The development and spread of antibiotic resistance (AR) in bacteria is a public health crisis.
- Antibiotic overuse in agriculture has created a large and diverse reservoir of resistant bacteria and resistance genes.
- Unless significant action is taken to turn the tide of AR, the daunting possibility that infections will no longer be treatable with antibiotics may be faced.

INTRODUCTION

The discovery and clinical implementation of antibiotics is one of the greatest achievements in the history of medicine. These miracle drugs treat infections ranging from minor to life threatening, enable surgeons to perform complex procedures in challenging anatomic locations, allow organ transplantation to be feasible, and empower oncologists to give higher doses of chemotherapy for cancer, thereby increasing the chance for cure. The global dissemination of AR bacteria, however, is threatening to undo all these advances and cause a return to the preantibiotic era.

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Approximately 2 million infections from AR bacteria occur annually in the United States, resulting in 23,000 deaths.[1] Moreover, these infections cause an increased risk of hospitalization and complications.[2] AR is an inevitable evolutionary outcome because all organisms develop genetic mutations to avoid lethal selective pressure (**Fig. 1**). As long as antibiotics are used against them, bacteria will continue to develop and use resistance mechanisms.[3] More than 70% of pathogenic bacteria are resistant to at least 1 antibiotic.[4] Notably, a recent survey of infectious diseases physicians in the United States found that 60% had encountered a bacterial infection resistant to available drugs in the previous year.[5]

AR is a complicated process that is driven by multiple factors (**Box 1**). Despite the global spread of AR, regulatory approval of new antibiotics has declined 90% during the past 30 years in the United States.[6] In addition to the high cost of antibiotic research and development, the rapid evolution of AR has meant diminished market returns for the pharmaceutical industry.[7] After many years out of the mainstream, the serious threat posed by AR has been increasingly recognized by the media and governmental organizations. For example, in September 2014, the White House proposed the National Strategy for Combating Antibiotic-Resistant Bacteria.[8] Herein, President Obama charged Congress with designing a research agenda to combat AR on multiple fronts.

The Centers for Disease Control and Prevention has prepared a list of AR bacteria in the United States that are of most concern (**Box 2**). Of these threats, the spread of AR gram-negative bacilli (GNB) is arguably the most worrisome. This is because of limited treatment options, the ease of plasmid-mediated transfer of resistance genes among GNB, the widespread distribution of Enterobacteriaceae as part of the human microbiome, the asymptomatic colonization present in certain individuals, and higher mortality associated with carbapenem-resistant Enterobacteriaceae compared with susceptible strains.[9] Moreover, risk factors have been identified for acquiring AR-GNB and include recent antibiotic usage, residence in extended care facilities, admission to an ICU, having an indwelling device or wounds, poor functional status, organ or stem cell transplantation, and travel to an endemic area.[10]

Of the drug classes to which AR can emerge, the most problematic is against the β-lactams. These are among the safest and most potent of antibiotics. β-lactam resistance in GNB is primarily acquired through plasmids that contain β-lactamases; β-lactamases are classified into 4 main groups based on their amino acid sequences (classes A, B, C, and D).[11] Class A includes extended-spectrum β-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemase enzymes, class B enzymes are the metallo-β-lactamases, class C enzymes are the cephalosporinases, and class D enzymes are oxacillinases. Recently it was recognized that *Acinetobacter baumannii*, although often considered a less virulent pathogen compared with *K pneumoniae* and *Pseudomonas aeruginosa*, plays a significant role in spreading broad-spectrum resistance genes to other gram-negative organisms.[12]

EVOLUTION OF ANTIBIOTIC RESISTANCE

The first effective antimicrobial agent, sulfonamide, was introduced in 1937. Within 2 years, sulfonamide resistance was reported and the same AR mechanisms are still clinically present more than 70 years later.[13] One useful way of understanding the basic mechanisms of AR is through the bullet and target concept, whereby the sites of drug activity (the target) can be changed by enzymatic modification, transformed by genomic mutations, and bypassed metabolically (eg, sulfonamide resistance);