Microbial Resistance: Bacteria and More

Martin J. Wood¹ and Robert C. Moellering, Jr.²

¹Department of Infection, Birmingham University, Heartlands Hospital, Birmingham, United Kingdom; and ²Harvard Medical School, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

The 20th century saw a series of remarkable discoveries that changed the face of medical practice. Among the most important was the discovery of antimicrobial agents, beginning with the synthesis of arsphenamine by Paul Ehrlich as the century dawned [1]. With this discovery, the dreaded scourge of syphilis was brought under control, although not eradicated. However, the toxicity of the drug made it less than ideal as an antimicrobial agent. Shortly thereafter, optochin (ethyl cupreine) was tried for therapy of pneumococcal pneumonia, but it too was toxic and was not effective enough to be successful. Moreover, pneumococci with resistance to this drug were isolated from patients who failed to respond to treatment—one of the first observations of antimicrobial resistance!

The middle of the century saw an even more remarkable set of discoveries: the development of the first true antibiotics, beginning with the sulfonamides and penicillin and progressing through a whole series of effective antimicrobials that attacked the bacterial cell at numerous vulnerable points. The discovery of effective antituberculous agents and antifungal agents soon followed. Viral infections provided a greater challenge, but even these have now yielded, at least in part, to the science of chemotherapy.

The luster of the antimicrobial era soon began to show evidence of tarnish, however, as first bacteria, then fungi, and then viruses began to develop resistance to the antimicrobial agents directed against them [1]. Microbial ingenuity and resilience have never been more evident than in their remarkable ability to develop resistance to chemotherapeutic agents. This is especially true of bacteria that have modified their DNA by chromosomal mutation and by acquiring resistance genes via conjugation, transformation, and even transduction. There are seemingly no boundaries to the capabilities of some microorganisms to develop resistance. The recent acquisition of vancomycin resistance in enterococci by the assembly of multiple foreign genes into transposable elements and the demonstration of transferable fluoroquinolone resistance genes in Klebsiella pneumoniae are 2 vivid examples of this [2, 3].

Antimicrobial resistance has been fueled by inappropriate use of antimicrobial agents—especially those directed against bacteria. Widespread industrial and agricultural use of antimicrobials has played a role, but the unwillingness of the medical profession to accept measures for the restraint or control of indiscriminate prescribing and inappropriate dosing of antibiotics needs to be addressed. Clinicians have failed to deal with a potentially solvable problem, and others are taking up the challenge. The inexorable spread of antimicrobial resistance is now of concern to agencies of numerous governments and health agencies worldwide, including the World Health Organization, which has attempted to bring order to chaos and provide rational solutions to the problem.

The 5 articles in this symposium provide insight regarding a number of important aspects of antimicrobial resistance. The first article, by Howard et al. [4], discusses the global impact of drug resistance. They note that although a number of previous studies have focused on costs, morbidity, and mortality related to infections caused by resistant microorganisms, most of these studies concentrate primarily on the infected patient. The authors emphasize that this is not the whole story and make the important observation that the true cost of antimicrobial resistance goes far beyond the individuals infected with resistant bacteria, fungi, or viruses. When the rates of resistance become high enough, physicians and others determining therapeutic policy change empiric therapy for a variety of common infections, including respiratory tract infections, malaria, and tuberculosis. The authors note that in some cases, the overall costs of these changes exceed those related to treatment failure.

Livermore [5] focuses on resistance in bacteria and discusses the plethora of mechanisms involved, including several that have only recently been discovered. He also notes that there are a number of elements in the epidemiology of bacterial resistance that are not fully understood. For instance, we do not know why certain
multidrug-resistant bacteria spread widely and others do not. He too makes the point that although there is not a perfect correlation between in vitro resistance and therapeutic failure, there is little doubt that resistance takes a heavy toll on society in terms of cost, morbidity, and mortality.

The problem of drug-resistant tuberculosis is discussed by Nachega and Chaisson [6], who trace the history of multidrug-resistant tuberculosis and note that this has become a global problem that threatens a number of countries in Europe, Asia, Africa, and the Americas. This is particularly true in nations with weak control programs and poor public health infrastructure. The authors discuss in detail the mechanisms of resistance to antituberculous agents and provide the rationale for multiple drug regimens in preventing the emergence of resistance during therapy. They point out that ultimately, management of multidrug-resistant tuberculosis relies on early diagnosis and teams of experienced personnel for treatment supervision—expertise that is often most lacking in the countries with the biggest multidrug-resistant tuberculosis problems.

Despite several new developments, there is still a shortage of effective agents for the treatment of invasive fungal infections, and the emergence and spread of resistance to antifungals is of increasing concern. In the fourth article of this supplement, Loeffler and Stevens [7] provide insights into the problems of resistance in fungi. They have provided a comprehensive account of the mechanisms of action of the major classes of antifungal agents and the multiple mechanisms of resistance to these agents that have evolved.

Drusano’s article [8], which concludes this symposium, addresses the impact of proper (or improper) dosing on the emergence of resistant strains during therapy of bacterial, fungal, and viral infections. He notes that it is possible to use pharmacodynamics principles to minimize the emergence of mutational resistance to agents including carbapenems, fluoroquinolones, the azoles, and the protease inhibitors. He also discusses the judicious use of combination therapy for prevention of resistance, something that has long been accepted in the treatment of tuberculosis but is now equally relevant to the treatment of HIV infection—and possibly will become important in the management of fungal infections.

It is clear that resistance to antimicrobial agents among bacteria, fungi, and viruses is a major threat to our therapeutic armamentarium. The articles in this symposium form a basis for understanding the impact of resistance and provide hope that we can use the scientific tools at our disposal to effectively combat it.

References