

The past few years have seen dire predictions of the appearance of the post-antimicrobial era. There have been dramatic headlines in the lay and medical press with lurid accounts of the untreatable super-bugs that stalk our streets and hospitals. In the future, we are told, we will have to learn to live without antimicrobials. To cap it, all the doom-mongers place the blame on irresponsible doctors. It is said to be all our own fault! This version of the future of antimicrobial therapy is inaccurate. It marries deeply hidden folk memories of past epidemic diseases with a legitimate concern about antimicrobial prescribing and the means to preserve the longevity of current anti-infective therapies.

History

The concept of an antimicrobial is a recent one. Indeed the concept of a micro-organism as the cause of what we now describe as infectious diseases—the germ theory of disease—is only 150 years old. It is true that quinine had long been available for the treatment of malaria in Europe since the mid-17th century, but there was no coherent understanding of its mechanism of action or against what it acted. Rather, it was seen that in a universe balanced by God, where a threat, malaria, was present, a solution, chinchona bark, would be found. It was Paul Ehrlich who made the first systematic account of the possibilities of specific antimicrobial medicines. His imaginative leap was to recognize that if his colleague, Robert Koch, could specifically stain *Mycobacterium tuberculosis* so that it could be identified in the sputum of patients with tuberculosis, then that specificity could be used to kill the organisms responsible for the disease. This led him to investigate specific dyes. There is a misunderstanding about his famous phrase “magic bullets”; it was not antimicrobial drugs that he described in that way but rather antibodies whose specificity he craved. Dyes active against trypanosomes, which were needed to curb the threat of sleeping sickness in Germany’s new colony in East Africa, were developed. During his research, Ehrlich noted that trypanosomes could develop resistance to the dyes that they were treated with. These same organisms, however, could also be successfully treated with dyes different from those to which they had developed the resistance. Further research on dyes led to the discovery of salvarsan, the first specific treatment against syphilis—Ehrlich’s crowning achievement.

Ehrlich’s approach to chemotherapy finally bore its full fruit with the development of Prontosil by Domagk. A whole series of synthetic compounds with activity against bacteria, most notably against *M. tuberculosis*, flowed from this research. But it was serendipity that brought about the most significant change. Fleming’s chance finding led to the discovery of penicillin. Initially, the difficulties of producing enough pure substance hindered the development of the drug, but the pressure of war stimulated a concerted drive to produce large quantities. Over the next 15 years, most of the main classes of antimicrobials were discovered.

Resistance

The significance of the fact that the first description of resistance coincides with Ehrlich's description of antimicrobial chemotherapy is often forgotten. In Fleming's original paper, he systematically describes the organisms that were intrinsically resistant to his new compound. The emergence of resistance is a natural consequence of the use of an antimicrobial agent. Improved living conditions in industrialized countries reduced the threat of infectious diseases, and year by year new drug discoveries overcame problem organisms as well as the resistance that was emerging. However, the significance of the threat posed by resistant organisms was recognized when one of the major pathogens tamed by penicillin became untreatable owing to resistance. The penicillinase-producing *Staphylococcus aureus* posed a significant threat to hospital patients. The solution was to modify the amido-penicillin nucleus, which resulted in ampicillin, and of more importance for the treatment of *S. aureus*, methicillin and its imitators. The subsequent decades saw an antimicrobial "arms race" as new agents were introduced to deal with increasing resistance among mainly Gram-negative pathogens. Falling research investment on the part of major pharmaceutical companies has reduced the number of new antimicrobials reaching the marketplace. Thus, with the appearance of glycopeptide-intermediate and later-resistant *S. aureus* (GISA, GRSA), glycopeptide-resistant *Enterococci*, and multiple drug-resistant *Acinetobacter*, *Stenotrophomonas*, *Klebsiella*, and *Pseudomonas*, the choice of antimicrobials to manage infections has become more difficult.

In the community, the first flush of antimicrobials remained for the most part effective. With the exception of *S. enteritidis* serovar Typhi, there were effective antimicrobials against the major community acquired bacterial infections. The first description of multiple drug-resistant *Streptococcus pneumoniae* and later intercontinental spread of resistant clones raised an alarm that was repeated with the explosive outbreaks of multiple drug-resistant *M. tuberculosis* in prisons and hospitals in the United States. A reduction in therapeutic choices has not been matched with new antimicrobial compounds for evaluation. The situation for both of these indications is bleak.

So have we reached the post-antimicrobial age? Not yet, for there are still therapeutic choices for most bacterial infections. It is true that clinicians managing infections in the hospital environment are now seeing with increasing regularity a small number of bacteria that are completely resistant to antimicrobials and these organisms occasionally cause infection. However, in most instances diligent application of sound clinical judgment allied with appropriate culture and susceptibility testing permits effective therapeutic regimens to be constructed. In the community, the antimicrobial treatment door has not yet closed, although we are all managing more cases where the therapeutic options are few, and in some cases none. Those of us who manage tuberculosis have had to revisit the old textbooks to relearn the natural history of untreated tuberculosis (untreated because it is untreatable) and to watch patients be slowly consumed by this inexorable disease.

We are not yet in the post-antimicrobial age, although we may fear that it is our final destination. It is a time when there are likely to be difficult therapeutic choices in every area of infectious disease practice. *Management of Multiple Drug-Resistant Infections*

is intended to provide practical advice about the management of multiple drug-resistant infections. Consequently, the focus has been on major hospital and community-acquired pathogens, including *S. aureus*, *S. pneumoniae*, *Acinetobacter*, and *M. tuberculosis*. In some parts of infection practice, managing resistance has become so much part of the fabric of life that it is no longer noticed. Thus, chapters on the management of multiple drug-resistant urinary tract infection and gonorrhoea have been included.

As Fleming initially observed in his first penicillin paper, some organisms are naturally resistant to antimicrobials; therefore, chapters discussing the management of some of these infections (naturally amphotericin-resistant fungi, nontuberculosis mycobacteria, and melioidosis) are included. Partly unrecognized by microbiologists in industrialized countries is the growing problem of resistance in *Plasmodium falciparum* malaria for more than one billion people who are at risk of infection by this pathogen. The extent of resistance problems extends to helminths and there is evidence that schistosomes are becoming resistant to the only drug effective against all of the species that infect humans. Antiviral agents are relative late-comers to the field of antimicrobial chemotherapy. As was the case for antibacterials, resistance to the antiviral drugs emerged rapidly. Two chapters have been included that address resistance among some of the most important antiviral classes: antiretrovirals and drugs that act against cytomegalovirus.

It is impossible to manage multiple drug-resistant infections without considering measures necessary to prevent spreading to other patients. It is for this reason that two chapters, one dealing with the epidemiology of tuberculosis and another dealing with the evidence base that supports infection control procedures, are included.

Antimicrobial and multiple drug resistance is a multifaceted problem that applies to almost all microorganisms for which science has developed drugs. The chapters selected are intended to reflect this diversity. In addition to providing scientific and epidemiological background, *Management of Multiple Drug-Resistant Infections* is also intended to be a practical guide to managing some of the most difficult infection problems with multiple drug-resistant organisms. I hope that those who have to wrestle with resistance every day will find it useful.

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