Int Microbiol (2002) 5: 97–99
DOI 10.1007/s10123-002-0070-3

BOOK REVIEW

Mercedes Berlanga

Kim Lewis, Abigail A. Salyers, Harry W. Taber, Richard G. Wax (eds): Bacterial resistance to antimicrobials

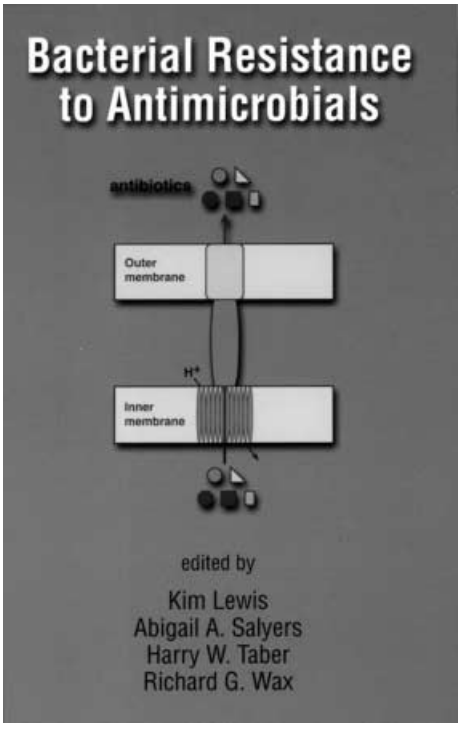
Marcel Dekker, New York, 2002. 496 pp. 23.5×15.5 cm (ISBN: 0-8247-0635-8) US$ 175.00

Published online: 29 May 2002

Most bacteria live in harmony with other inhabitants of the earth. When a bacterial infection occurs, in most instances it is the result of the entry of bacteria into the body by chance. Antibiotics were initially developed for the treatment of infectious diseases in people, but their miraculous effects led to their use in animals and plants. Antibiotics are used both internally and externally to control bacterial infections, maintaining the health of people, animals and agricultural crops. Over the last 60 years relationships between bacteria and people have vastly changed. Today we are witnessing another change, that is, among bacteria themselves.

From time to time, microbiologist and clinicians interested in infection have taken stock of the problems of antibiotic resistance and have summarized current knowledge. *Bacterial Resistance to Antimicrobial* describes our present understanding of the nature of antimicrobial resistance and the methods by which bacteria gain these defenses. Prior to the introduction of antibiotics, natural populations of human/animal bacterial pathogens or commensal bacteria were susceptible to antibiotic. This is known because analyses of collections of bacteria dating from the preantibiotic era fail to show resistance to the antibiotics commonly used in infectious disease therapy. Every time a person is treated with an antibiotic, that person's normal microbiota (commensal) is treated as well as the target pathogen. Actually, commensal bacteria might serve as reservoirs for resistance genes that could be transferred to pathogenic bacteria. At present, a high proportion of these pathogenic bacteria are functionally resistant to most of the antibiotics that have been used extensively during the "antibiotic era".

Almost as soon as it was known that microorganisms could be killed by certain substances, it was also recognized that some microbes could survive normally lethal doses of these same agents. The first clinical report of acquired resistance to an antimicrobial agent was published in 1937, when Crean, a naval genitourinary specialist, reported in *Lancet* that six of 100 patients with gonorrhea were unresponsive to treatment with sulfonamides. Reports of resistance to penicillin appeared in 1941, and to streptomycin in 1946. From about that time (1950s) the term "antibiotic resistant" acquired a clear meaning with a direct logical link between clinical and microbiological phenomena, although it has always been difficult to demonstrate the connection in practice because of the many confounding



M. Berlanga
University of Barcelona
E-mail: berlanga@ubxlab.com

factors that determine the course of an infection and because technical difficulties associated with the measurement of in vitro susceptibility to antibiotics. Gould wrote in 1960 ''We are as yet at an elementary stage in correlating the clinical administration of antibiotics with in vitro sensitivity determinations.''.

The introduction of an antibiotic into an environment (including the human body) has the eventual effect of killing off most, if not all, of the resident susceptible strains. But sometimes, resistant survivors are able to propagate and take over. Antibiotic resistance exemplifies par excellence the theory of Darwinism. A selective process (presence of antibiotics in the environment) leads to proliferation of resistant organisms. The selective pressure refers to the many factors that create an environmental landscape allowing organisms with novel mutations or newly acquired characteristics to survive and proliferate. Note that organisms resistant to antibiotics were resistant before antibiotics were administered. Antibiotics are not mutational agents but selective agents. Five properties characterize the acquired bacterial response against antibiotics: (a) Diversity, bacteria may respond through several different mechanisms of resistance, usually observed in the same species but also in different genera. (b) Promiscuity, bacteria respond as a global organism by the exchange of genetic information, such as conjugation, transformation and transduction. (c) Rapidity, bacteria can adapt quickly depending on the strain and the antibiotic. (d) Persistence in the environment, a dogma that has been widely accepted until recently is that antibiotic-resistant bacteria are always less fit in the absence of antibiotic selection than susceptible strains; but some studies have indicated that at least some resistant bacteria may be fit enough to persist for long periods of time. The persistence of resistant strains raises the question of whether antibiotics are the only selection pressure involved in maintaining resistant strains in the environment. (e) Novelty, ''new genes'' are brought into play; they were not available in the previous history of any bacterial species and they seem to appear spontaneously.

Bacterial Resistance to Antimicrobial is structured in 18 chapters written by different authors. Chapters 1–3 (''The ecology of antibiotic resistance genes'', ''Antibiotic resistance: how bacterial populations respond to a simple evolutionary force'' and ''Global response systems that cause resistance'') constitute a general introduction to antibiotic resistance. Different topics are developed such as antibiotic use in agriculture and hospitals, persistence of resistance genes in the environment, concepts of antimicrobial susceptibility and resistance, and characteristics of bacterial acquired resistance. Chapter 3 introduces interesting thinking: antibiotics themselves may be but the tip of the iceberg, covering just another hidden aspect of microbiological nature, the social life of microbes. This is another example of biological serendipity by which an unrelated observation uncovers new subjects of inquiry: what is the role of antibiotics in nature? Are bacteria really organized in networks of communicating organisms (in relation to biofilms)?

Chaptes 4–9 (''Drug efflux'', ''Mechanisms of aminoglycoside antibiotic resistance'', ''β-Lactamase and resistance to β-lactam antibiotics'', ''Target modification as a mechanism of antimicrobial resistance'', ''Antibiotic permeability'' and ''Phenotypic tolerance of bacteria'') focus on the study of resistance mechanisms in bacteria. Alteration of the target of an antimicrobial drug is a widely used bacterial mechanism of drug resistance and, in addition to permeability alteration – both reduced permeability and increased efflux – and drug modification by enzymatic activity, is one of the three major resistance mechanisms. Modification often results in the alteration of the original drug's target structure such that it binds the antibiotic poorly or not at all. This alteration in structure can be due to spontaneous mutations in the gene(s) encoding the target that modify single or limited numbers of amino acids, often in the region of the drug-binding site. Resistance by efflux of antimicrobials agents is widespread in the bacterial world. Multidrug resistance pumps (MDRs) are capable of recognizing multiple antibiotics with amphiphilic and positive charge characteristics. The ability of antimicrobial compounds to enter bacterial cells generally is a prerequisite to their antibacterial action. The mechanisms for entry of antimicrobial agents very widely depending upon the chemical nature of the agent and the characteristics of the bacterial cell envelope. Resistance is associated with specific variations or alterations in envelope structure.

Chapters 10–17 (''Resistance as a worldwide problem'', ''Genetic methods for detecting bacterial resistance genes'', ''Resistance problems associated with the enterococcus'', ''Evolution and epidemiology of antibiotic-resistant pneumococci'', ''Methicillin resistance in *Staphylococcus aureus*'', ''Drug resistance and tuberculosis chemotherapy – from concept to genomics'', ''Antibiotic resistance in enterobacteria'' and ''Public health responses to antimicrobial resistance in outpatient and inpatient settings'') provide an overview of resistance in the major global infectious diseases and summarize the factors contributing to the emergence and spread of resistance. Despite the major medical advances of the last century, infectious diseases still account for 25% of all deaths and up to 45% of deaths in developing countries. Although the appropriate antimicrobial agents are available, the emergence of antibiotic-resistant strains may prevent effective combat of these diseases. Antimicrobial resistance increases the mortality and morbidity due to infectious disease and has an important impact on the cost of health care. These consequences result from the accumulation of resistance determinants by microbial pathogens, thereby reducing the treatment options and enhancing the spread of resistant strains from person to person. The spread of resistance can be ''compartmentalized'' within a community (e.g., person to person, animal/food to person) and in hospitals. In the past, these two

compartments have tended to harbor different pathogens and different resistance problems. For example, sepsis caused by multiresistant gram-negative or gram-positive bacteria is found almost exclusively in hospital patients, whereas antimicrobial-resistant sexually transmitted infections and diarrheal disease are community problems. At present, this separation is not so obvious, as there are no ''barriers'' to microbes and they can easily change compartments or niches. For example, the early discharge of hospital patients contributes to the spread of hospital microorganisms into the community, and the increasing spread of resistant ''community'' pathogens in other ''closed'' situations (e.g., day care centers, prisons) to the hospital. The enormous increase in international travel and trade has enabled the rapid globalization of resistance.

Chapter 18 (''Approaches to new antimicrobial targets in the age of genomics'') describes approaches to new antimicrobial targets. The traditional targets exploited by the pharmaceutical industry for discovery of new antibiotics have largely been limited to enzymes or structural proteins involved in the well-characterized major essential pathways of macromolecule biosynthesis, including protein synthesis, production or assembly of cell wall peptidoglycan, and DNA synthesis. We must develop a screen for ''novel essential'' targets, to which even multidrug-resistant organisms are susceptible.

Bacterial Resistance to Antimicrobial provides excellent, useful, modern source material about antibiotic resistance and its epidemiology. The ultimate goal of this information is to provide guidelines for creating antibiotics effective against refractory strains, and to offer strategies to minimize the emergence and spread of resistance. Combating antibiotic resistance will require the combined efforts of many sectors of our society: doctors, the pharmaceutical industry, patients, and government. *Bacterial Resistance to Antimicrobial* is especially recommended to physicians and clinical microbiologists. ''If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties'' – Francis Bacon, *Advancement of Learning*.