A Recent History of Antibiotics
And Where We May Be Going
Introduction

Historically, we tend to be a rather smug group – microbiologists and infectious disease physicians! Pre-1970’s we were quite pleased with ourselves because we thought we knew all about the agents of infection and we had a significant arsenal of treatments to use against them. We had 14 classes of antibiotics providing over 100 individual antibiotics to treat infected patients. Yes, there was that worrisome methicillin-resistant Staphylococcus aureus (MRSA) out there but even with that organism we had our weapons such as sulfa drugs, tetracyclines and clindamycin. Little did we know that MRSA would soon become multiple-resistant MRSA and within 20 years become endemic in the population – and not just the hospitalized population.

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Our confidence started to erode in the late 70’s and early 80’s. In 1976 a group of Legionnaires had a convention in Philadelphia, PA. People began to get sick and some died of an obvious infection but of unknown origin causing a type of pneumonia, unresponsive to the usual treatments for pneumonia used at the time. This was not supposed to happen! It was an intense wake-up call to the medical and research community and a portent of things to come. By 1981 we were seeing the first cases of AIDS. The agent of this strange disease caused multiple symptoms but most devastatingly it crippled the immune system. The agent, HIV, was finally characterized in 1983 by Gallo and Montagnier. The patients infected with HIV often got Kaposi’s sarcoma and a series of (until then) rare and unusual opportunistic infections. These included fungal infections such as candidiasis of the trachea and esophagus, Mycobacterium avium complex, and cytomegalovirus (CMV). With the emergence of these and other new infections we were also seeing increased resistance to antibiotics.

As the decade of the 1980’s progressed so also did the number of gram negative organisms resistant to the most common antibiotics. Both linear and vertical antibiotic resistance transfer was taking place. During the late 1970’s and early 1980’s pharmaceutical companies were divesting of their antibiotic research and moving into more lucrative areas of product development such as cardiovascular drugs.

(Some of you may remember that pharmaceutical companies would receive soil samples from all over the world to be screened for new organisms that could produce antibiotics!) While the bacteria were silently becoming more resistant to antibiotics, we were losing ground rapidly in the development of more successful antibiotics. In a presentation at an American Society for Microbiology meeting during that period, Dr. Stuart Levy at Tufts Medical School and an Infectious Diseases expert indicated that we were as much as four years behind the organisms in development of useful antibiotics. Why was all of this happening with regard to development of resistance? First, we need to be clear – use of antibiotics does NOT cause antibiotic resistance. Antibiotic use (or misuse) screens for resistant organisms that are already in the environment or in the host; they don’t make resistant organisms. (Louis Pasteur proved that spontaneous generation does not exist!) As an example, there are a number of documented reports that there were organisms stored away prior to the discovery of penicillin by Alexander Fleming in 1928 that were found to be resistant to penicillin. Organisms produce resistance factors during their normal growth and replication. We help this process along by using antibiotics that inhibit “usual” susceptible organisms that, by their large numbers would ordinarily over-grow and inhibit growth of resistant organisms. Thus, we allow the resistant organisms to become the prominent organisms.
The increasing resistance we see today is enhanced by use of antibiotics when they are actually not needed, such as when you have a viral infection or a minor injury. Hand washing is one of the easiest and most effective methods of eliminating or decreasing spread of organisms. Multiple strategies have been employed to control the spread of these resistant organisms. Strategies to limit antibiotic resistance include increased adherence to infection control measures, therapeutic antibiotic substitution, prudent prescribing of antibiotics, and pharmacy-based computer antibiotic management programs. In addition, the cycling or rotation of antibiotics for empirical therapy has been examined as a method for preventing the development of antimicrobial resistance. Many of these ideas are not new but data as to efficacy is not complete or relatively old and not reflecting newer practices.

As already indicated, prior to 1970, 14 classes of antibiotics were introduced. Since then only five new classes have been introduced as depicted in the Figure below. The approval of new individual antibiotics by FDA is also telling (Figure below). From 1980 to 1989, 29 new antibiotics were approved by FDA. From 1990 to 1999, 22 new antibiotics were approved. From 2000 to present (2012) only 11 new antibiotics were introduced. A more striking figure is that only 3 new antibiotics were approved by FDA from 2007 to 2012. It is obvious that we are still losing ground to the antibiotic resistant organisms.

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In a report by the Robert Wood Johnson Foundation (2008), it was stated that the current antibiotic pipeline lacks diversity in the range of diseases at which new drugs are aimed.
Studies in which our ClinicalRM researchers are involved are trying to address some of these issues. New antibiotics are being developed with at least five new candidates currently in the pipeline for testing over the next year. In our cooperative clinical trials with NIAID and several universities, we are researching alternative uses of old antibiotics such as colistin and the efficacy of new antibiotics.

Another strategy is the development of more and better resistance-modifying agents. For example, some resistance-modifying agents inhibit multiple drug resistance mechanisms, such as drug efflux from cells, thus increasing the bacteria’s drug susceptibility. Of themselves, these agents often do not have antimicrobial activity but when added to the antibiotic, will enhance the activity of the antibiotic. An example would be the beta-lactamase inhibitors such as clavulanic acid and sulbactam.

There are alternatives to antibiotics other than those indicated above including research into bacteriocins which are peptides or small molecules that have antibiotic-like activity but tend to have a narrow spectrum of activity and require prior diagnostic identification of the infectious agents prior to use.

Currently under investigation and of interest to the military and ClinicalRM researchers, is bacteriophage therapy. Bacteriophage are viruses that attack bacteria. Although sounding a bit like science fiction, the concept of using viruses that attack only the bacteria and not the human host has been in existence since the 1920’s. Because of the problems associated with antibiotics, there is renewed interest in this potential modality, especially for open wound infections.

Several of our researchers for the Government are interested in the development of chelators that would limit or eliminate the availability of essential components of metabolism for the bacteria. An example of a target for chelating agents is iron which is required for growth of many bacteria.

ClinicalRM researchers have been at the forefront of the development of vaccines for many infectious agents for nearly two decades. During the last 20 years in our work with the WRIAR, USAMRIID, and NIH we have addressed biological agents of disease with vaccines and antimicrobials. We too have seen changes over the two decades. Initially our work focused on tropical diseases that faced our warfighters such as malaria, Leishmania and dengue. As the century dawned we found ourselves on the leading edge of research involving biological threats to our warfighters and the world at large such as anthrax, ricin, and the potential re-emergence of smallpox. Most recently we have been working on the worlds newer threats of pandemic influenza and West Nile. The emergence of newer threats has also increased our work in surveillance and epidemiology.

Infectious disease is, and continues to be, our leading therapeutic area of work. While continuing to support our long term commitment to tropical diseases, we are actively evolving and pursuing additional work in the bio-threat arena and doubling our efforts in the emerging disease and surveillance areas to best serve the needs of our military and government customer’s needs.
About Clinical Research Management, Inc.
Clinical Research Management (ClinicalRM) is not only involved in the testing of new antibiotics in Phase I, II, III studies, monitoring protocol development, site selection, and assistance with FDA approvals, but is also involved in responding to the challenges of antimicrobial resistance. Our epidemiologists track resistance patterns around the globe and they evaluate how the observed resistance appears, where it emanates from, and how we can best contain the spread of the new resistance factors.

Our scientists work with the Government and academia to develop new responses to the ever-growing threat of multiple-resistant superbugs. They use in silico techniques, as well as information from genomics, to determine sites on, or in, these organisms that are most likely to be vulnerable to engineered antimicrobials. ClinicalRM is committed to developing new responses to disease and the challenges presented by these super-bugs. If you feel ClinicalRM can add value to your research efforts, we are interested in speaking with you. Call toll free at (800) 431-9640 or visit www.clinicalrm.com

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You can read more of Dr. Boyer’s writings at www.clinicalrm.com