Antibiotics and the Reemergence of Bacterial Disease

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Since their discovery and widespread medicinal application, the first antibiotics have gone from “magic bullet” to inevitably obsolete. The health problems posed today by antibiotic resistance are extensive, and their intersection with the chemical sciences is pronounced. The following describes both the positive and negative impact that antibiotic development has had on our society, and it includes a brief overview of some of the causes. The discussion concludes with a condensed case study looking at synthetic modification and hybridization of antibiotics in an effort to underscore the importance of medicinal chemistry in confronting today’s health problems.

History

The Sulfonamides (Sulfa drugs) were discovered in 1935 by the German physician and chemist Gerhard Domagk and were the first class of antibacterials commercially available. Sulfa drugs do not provide an ideal method for treating bacterial infection due to their limited efficacy and high propensity to induce major allergic reactions, but during the 1930s, in the absence of other treatments for infection, the use of sulfa drugs exploded. Although credited with saving tens of thousands of lives, including that of Winston Churchill, the greatest contribution of sulfa drugs may have been their effect on public policy. By the late 1930's countless forms of sulfa drugs were being produced by dozens of manufacturers. One of these drugs, Elixir Sulfonamide, was prepared using a toxic chemical that caused the deaths of more than 100 people. In response to this tragedy, Congress passed The Federal Food, Drug, and Cosmetic Act of 1938, that gave the United States Food and Drug Administration authority to oversee the safety of drugs as well as food and cosmetics.

While Sulfa drugs played a central role in preventing infections throughout World War II, it wasn't until the 1940's that the antibiotic age took full flight. The term antibiotic was coined in 1942 by Salman Abraham Waksman, a professor at Rutgers University; by 1945, antibiotics were widely available. Among the first of the new drugs was penicillin. Penicillin offered effective treatment against a myriad of previously untreatable diseases and had limited side effects. Penicillin was indeed the wonder drug of the 20th century. New antibiotics were quickly produced and it appeared that the problem of bacterial disease was solved. However, this was not the case, and while science was taking a victory lap, the battle against bacterial disease was just beginning.

The Human Toll

The impact that bacterial resistance has on our society is profound. In a 2013 report released by the Center for Disease Control, it was conservatively estimated that there were over two million severe cases of antibiotic resistance per year in the United States, causing twenty-three thousand deaths a year (5).

In addition to the human cost, there are major economic concerns. Antibiotic resistance extends recovery time and, in the United States, results in approximately 20 billion dollars in additional health care costs each year and 25 billion dollars a year in lost productivity (5).

The dangers presented by antibiotic resistance are not limited to bacterial infection itself. As the incidence of antibiotic resistance grows, so does the use of antibiotics, and this increase in antibiotic use comes with a cost. Almost one out of every five emergency room visits is attributed to antibiotics (5). Some of the major side effects of antibiotic drugs are allergic reactions, diarrhea, and adverse interaction with other medications. Another problem with antibiotics is that they affect all bacteria indiscriminately; destroying the bacteria that are beneficial for our digestive system. For example, C. difficile is an infection that occurs following antibiotic treatment once the normal flora in the colon have been wiped out. C. difficile bacteria are not necessarily dangerous by themselves but, in the absence of beneficial bacteria, C. difficile bacteria can grow out of control, causing symptoms ranging from diarrhea to life-threatening inflammation of the colon. Each year in the United States over 250,000 people are hospitalized with C. difficile, 14,000 of whom die (5).

The Problem

Antibiotic resistance itself is not a new phenomenon. Natural-product antibiotics have been estimated to have originated between 40 million and 2 billion years ago, suggesting that

resistance should be similarly old (6). The concern is not that antibiotic resistance exists but that the pace at which it is adapting to our treatments seems to be increasing. New classifications of diseases include MRSA (Methicillin-resistant Staphylococcus Aureus), VRE (Vancomycin-resistant Enterococci) and other MDR (multi-drug-resistant) strains of bacteria and, to make matters worse, development of new antibiotics has steadily slowed since the 1940's, as shown in figure 1.

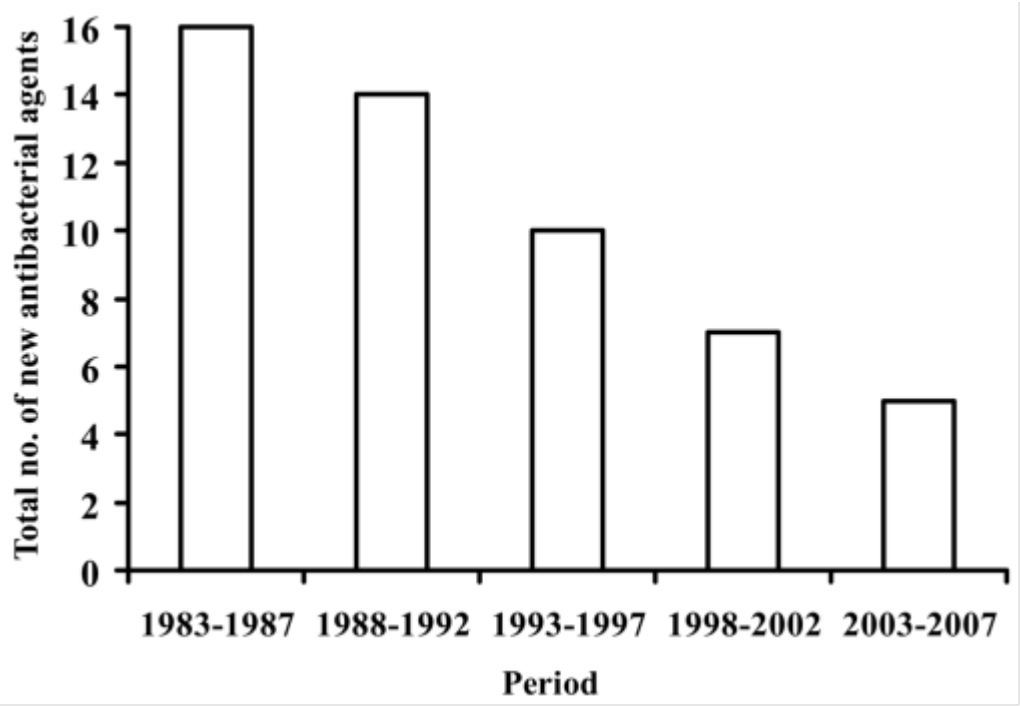

Figure 1*: Systemic (i.e., nontopical) antibacterial new molecular entities approved by the US Food and Drug Administration, per 5-year period (1)*

The slow-down in development of antibiotics can be attributed to numerous factors. One point of view suggests that we have exhausted the low-hanging fruit. While this may true, it doesn't tell the whole story. The problem, as the World Health Organization points out, is that "Antibiotics, in particular, have a poor return on investment because they are taken for a short period of time and cure their target disease. In contrast, drugs that treat chronic illness, such as

high blood pressure, are taken daily for the rest of a patient's life" (8). In the absence of financial incentives, major drug manufactures have become increasingly less interested in antibiotic development. A 2012 article in Forbes Magazine estimates the average cost of a drug developed by a major pharmaceutical company is near four billion dollars (4).

Antibiotics are unique among pharmaceutics in that they precipitate their own obsolescence. Evolution prompts the selection of infections that are able to circumvent antibiotic treatment. This process limits the effective lifetime of any medicinal agent. It is important to understand that antibiotic use, not resistance itself, is the principal cause of the health problems that result from antibiotic resistance. Confronting this problem will require more than just continued development of new drugs.

The cause

Antibacterial resistance is intrinsically connected to society; a complete understanding of that problem requires more than an acknowledgement of evolutionary characteristics. Our overuse and misuse of antibiotics perpetuates and accelerates bacterial resistance to antibiotic treatments.

As individuals we can take steps to correct overuse and misuse. An article in the San Francisco Chronicle points out that, "Repeated warnings that antibiotics don't work for most sore throats and bronchitis have failed to stop overuse" (3). It's important to understand that antibiotics treat bacterial, not viral infections. When treatment is necessary, it is especially important to complete treatment. Many individuals cease treatment once they feel better. While symptoms may stop, premature termination of antibiotic treatment allows the infection to re-

emerge, and when it does, it will likely bring with it a resistance to the antibiotic originally used to treat it.

A Brief Look at Synthetic Chemistry

Synthetic chemistry provides one method of confronting the problem of antibacterial resistance. Synthetic medicinal chemistry plays a significant role in antibiotic development, but any comprehensive solution will involve an interdisciplinary approach. The following case study highlights how modifying existing antibiotic classes and hybridizing antimicrobials can aid in confronting antibiotic resistance.

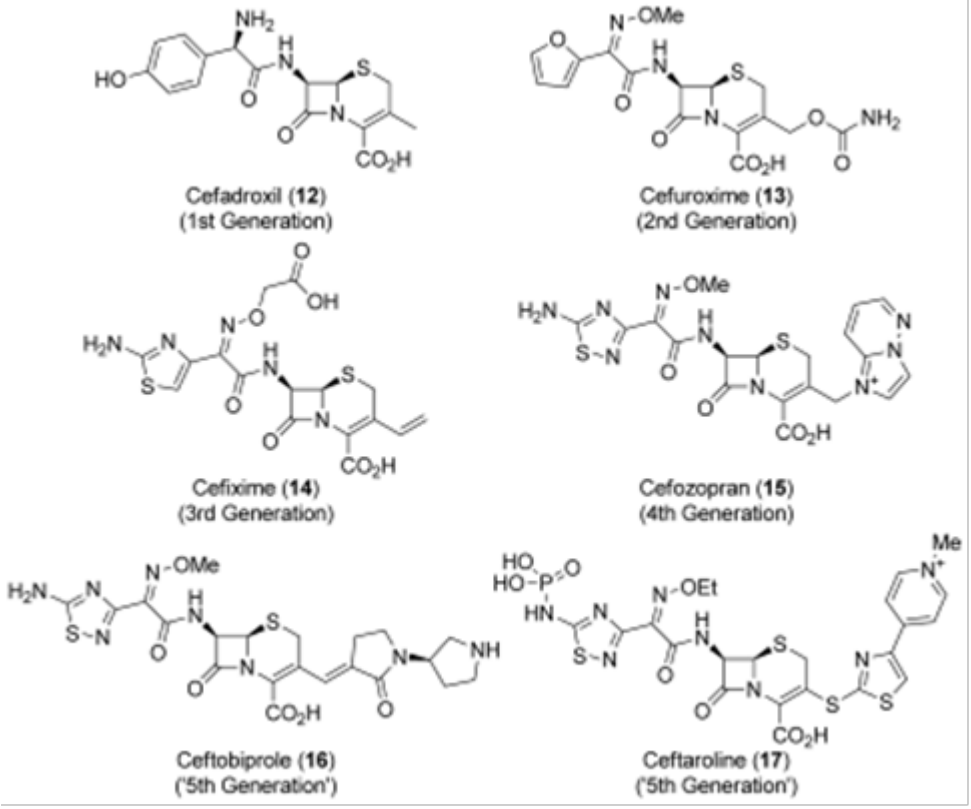

***Figure 2**: Different generations of cephalosporins (2)*

Rather than create new classes of antibiotics, synthetic modification of existing classes uses minor molecular changes to effect major biological results. The Cephalosporins are a class of antibacterials that have received extensive modifications over the years and "The broad activity spectrum, proven efficacy, and favorable safety profile of this class has made it one of the most widely prescribed clinical classes" (2). Cephalosporins are used to treat an extensive list of infections including pneumonia, strep throat, staph infections, tonsillitis, bronchitis, and gonorrhea. Further, fifth generation cephalosporins are active against multidrug-resistant diseases such as MRSA (7). Figure 2 shows first, third, and fifth generation cephalosporins. Subsequent generations of cephalosporins are not exclusionary, meaning that new generations do not render the parent generations obsolete but instead provide varying efficacy and activity spectra.

Vancomycin provides another example of the role medicinal chemistry can play in confronting antibacterial resistance. Tolerance to these toxic antibiotics is not increased by exposing the patient to related substances; as a result, vancomycin is often considered a last resort in multi-drug-resistant infections. As antibiotic-resistant strains of bacteria such as MRSA have become more prevalent so has the use of vancomycin. Not surprisingly, as a result of its increased use, vancomycin-resistant strains have steadily increased since their initial discovery in 1988. The first and probably most widely recognized form of vancomycin-resistant bacteria is VRE.

The mechanistic process that Vancomycin follows to incapacitate a bacterial infection is different from that of the cephalosporins, but the end result is similar. During replication, a bacterial species must synthesize a new cell wall that prevents bacteria from lysing (exploding). To produce a new cell wall, a bacterium must both produce specific peptide chains and cross-link

them. Vancomycin works by binding to the ends of these peptide chains, preventing linkage, resulting in lysis of the cell. Binding of vancomycin occurs as a result of five specific hydrogen-bond interactions shown in figure 3.

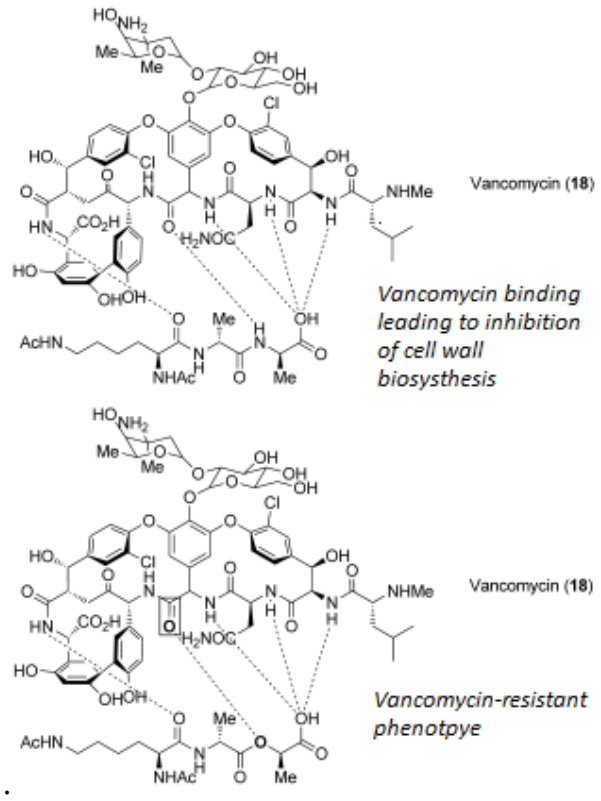

Figure 3*: Vancomycin resistance resulting from the substitution of D-Ala-D-Ala for D-Ala-D-Lac (2).*

The most common vancomycin resistance is a result of a single NH –to-O substitution at one of the binding sites of the bacterial species. This substitution results in a 1,000-fold reduction in the binding affinity between vancomycin and bacteria due to an interaction between the lone pair of electrons. Synthetic techniques allowed researchers to explore this interaction and to improve bonding affinity. Figure 4 shows two Vancomycin analogues 19 (removal of the carbonyl oxygen atom) and 20 (replacement by the amine functional group).

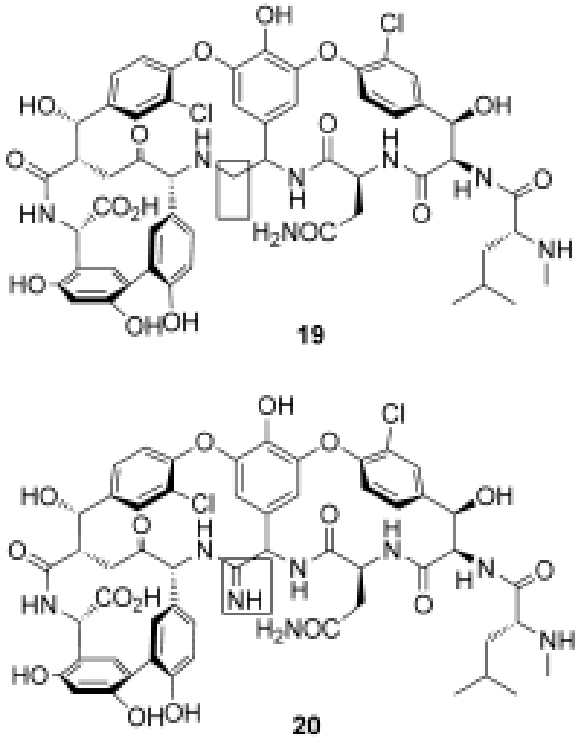

Figure 4: Vancomycin aglycon analogues synthesized by Boger and co-workers (2).

Hybridizing antimicrobials aims to produce a single biofunctional entity that bears an activity spectrum greater than those of its individual substituents. The hope is that, by combining two different antibiotics, with two different efficacy profiles into a single antibiotic that exhibits the efficacy profiles of each, bacterial resistance will emerge more slowly. Historically, these programs have been overwhelmingly unsuccessful, but while many research programs have been abandoned, research into this area of medicinal chemistry continues.

Over the last fifty years wide application of aminoglycosides (a class of antibiotics) has resulted in a variety of resistance mechanisms limiting their usefulness but hybridization with fluoroquinolone, another antibiotic, shows promise. While fluoroquinolone–aminoglycoside antibacterials are considerably less potent than their parent species, the hybrids exhibit one major advantage. When assessing the propensity to induce drug resistance, the hybrid proved to be

more desirable, producing antibacterial resistance more slowly than either ciprofloxacin or neomycin alone (2).

Hybrid antibacterials are not limited to the fusion of different anti-bacterial species. Antibiotics have been combined with iron(III)-chelating siderophore groups as shown in figure 5. These antibiotic hybrids have the potential to overcome obstacles posed by the cell envelope (a complex multilayer structure that surrounds and protects bacteria) in antibiotic-resistant species of bacteria. Because many bacteria actively transport FeIII–siderophore complexes into the cell, an antibiotic-siderophore hybrid has the potential to function as a "Trojan Horse" compound. Although further investigation is necessary, a recent study has produced encouraging results. A study comparing the iron complex and its parent species found that the complex required a far smaller concentration to inhibit bacterial growth than the non-hybridized species (2).

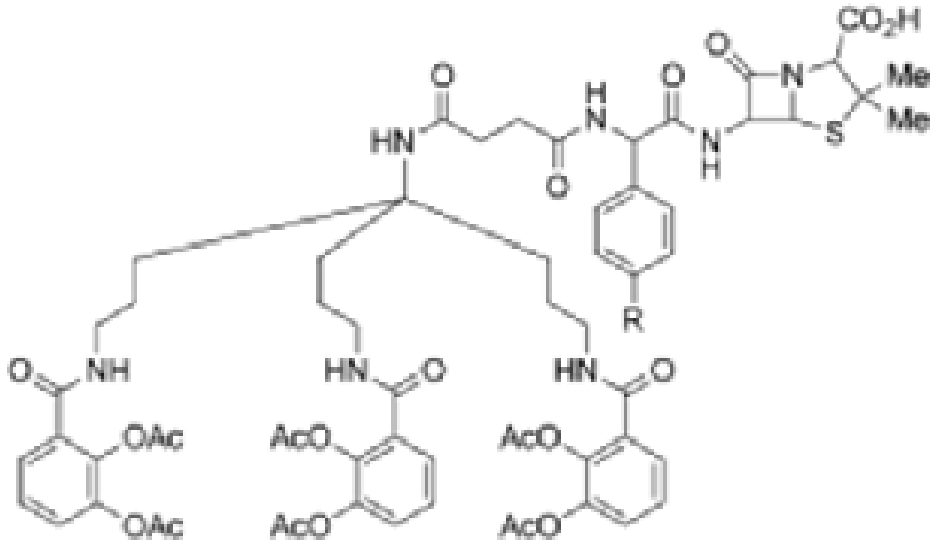

Figure 5: Penicillin–siderophore conjugate by Miller et al (2).

Concluding Remarks

The importance of an interdisciplinary approach is the only truly comprehensive method of addressing antibiotic resistance. We have seen two different techniques within synthetic chemistry that may allow us to address antibiotic resistance. Today, research spanning the sciences, from biology to computer science, are coming together to confront the problem, but even complete cooperation within the sciences is not enough. Antibiotic resistance is an intrinsic component of antibiotic use; making both the idea of a “magic bullet” unreasonable and our continued vigilance essential. We must keep in mind that the problem of antibiotic resistance is, first and foremost, a human problem, and as such, will require the participation of the humanities in order to solve it. We need laws to discourage misuse and abuse of antibiotics, as well as those that encourage new drug development. We need to engage in discussions that will educate and encourage individual responsibility. The advent of antibiotics has been one of the most important advances in chemical technology, but with this great power comes a new set of challenges and responsibilities.

Referances

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