Credit: MRSA - CDC Podcasts (2007); Biohazard Symbol - http://ecfr.gpoaccess.gov/cgi/

Antibiotic resistant bacteria: The continuing fight

By Seth Cassel

Forty years ago, the fight against disease-causing bacteria seemed to have been won. The creation of antibiotics had rid the human race of some of its most deadly foes. Even the US Surgeon General, in 1967, felt that it was time to "close the book on infectious disease" (1). Tell that to the families of the 19,000 people who die each year from infection by Methicillin-resistant Staphyloccocus aureus (MRSA), one of the deadliest antibiotic-resistant bacteria in existence (2).

The development of antibiotic-resistant bacterial strains is the same story touted ad nauseum in the popular news – doctors overprescribe antibiotics and patients do not take their medicine for the full course. This combination increases bacteria's exposure to a drug and allows mutated strains to escape death and perpetuate - "naturally" selecting for antibiotic resistant strains. The solution? In the past, it seemed obvious. Norman Simmons, emeritus consultant microbiologist from Guy's Hospital, London, suggested in 1998 that "we should just use [antibiotics] less" (3). But over 10 years have passed, and the problem continues to grow: constantly mutating bacteria have surpassed the capabilities of our static arsenal of antibiotics (2).

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Around 19,000 people die every year from MRSA – a fatality rate higher than that of HIV/AIDS – and the number is growing (2). MRSA is just one example of antibiotic-resistant bacteria, and it is part of a growing trend, causing some, like Professor Richard James of Nottingham's Institute of Infections, Immunity, and Inflammation to say that we are entering "a post-antibiotic apocalypse" (4). Regardless of one's feelings about such rhetoric, James's sentiment is based in reality – difficult-to-treat infectious diseases are on the rise as more strains of bacteria become resistant to antibiotics (2). However, scientific research is well underway to find methods to fight this new generation of deadly bacteria.

How it all started

Modern antibiotic use first came about in 1909 when Paul Ehrlich discovered an arsenical compound called Salvarsan, targeted at treating syphilis. Later on, antibiotic development was

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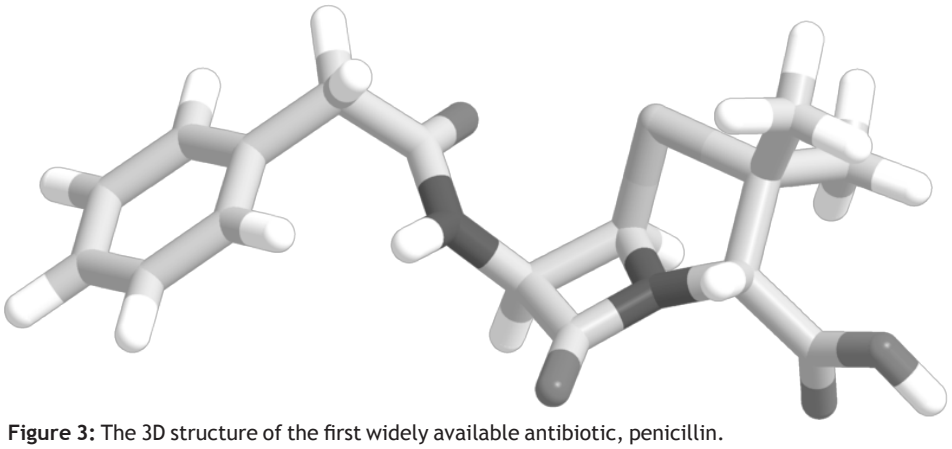

Figure 3: The 3D structure of the first widely available antibiotic, penicillin.

accelerated by Ernst Fleming's discovery of penicillin in 1928, and its purification by Ernst Chain and Howard Florey. Penicillin was used with great efficacy in treating ailing soldiers during World War II. In 1932, Gerhard Domagk developed the sulfonamide Prontosil, which became the first commercially available antibiotic with broad applicability.

There are currently three major categories of antibiotics, classified by the method used to fight disease-causing bacteria (5). The first are antibiotics, like penicillin, which prevent cell wall synthesis and lyse the cell. Another group is comprised of inhibitors of protein synthesis, such as tetracycline, which bind to the ribosome, preventing translation of mRNA into protein. The last category inhibits the synthesis of DNA replication in a variety of ways. For example, the sulfonamide Prontosil is a competitive inhibitor of one of the enzymes involved in the synthesis of folic acid and thus serves to hinder bacterial DNA synthesis (5).

Bacterial methods of resistance

In order to escape the effects of antibiotics, bacteria have adopted different strategies. The simplest is the acquisition of antibiotic resistance through random mutation. Another bacterial strategy is to replace or alter the target site where the antibiotic binds so the drug can no longer attach to this site (2). Other bacteria gain antibiotic resistance by producing enzymes that attack the antibiotic in order to destroy or modify it, rendering the drug ineffective (2). Alternatively, some bacteria have gained new functionality through horizontal gene transfer (2). Bacteria swap genetic information through circular pieces of DNA called plasmids, which can be sent from one bacterium to another and can be copied into the recipient's genome. As bacteria acquire more and more antibiotic-resistant genes from other bacteria, horizontal transfer is allowing for some of the most virulent bacterial strains observed today (2).

The current situation

Most antibiotics used today were developed between the 1940s and 1960s. Since then, new drug development has mainly been in the form of chemical modifications on existing antibiotics' scaffolding. This lull in new drug development is largely because antibiotics for the easiest bacterial targets have already been identified (2), and also due to the fact that the pharmaceutical industry has greatly decreased its antibiotic research efforts, as drugs for long-term diseases, such as depression, are more lucrative (6).

A relatively stagnant supply of new antibiotic drugs left the door open for the evolution of virulent strains of antibiotic-resistant bacteria, most notably Methicillin-resistant Staphylococcus aureus (MRSA). According to Henry Chamber, an infectious disease specialist at the University of California, San Francisco, typically 1 - 5% of S. aureus strains identified in hospitals in 1980 were resistant to methicillin, but that number has grown so that today, 60-70% of S. aureus strains found in hospitals are methicillin-resistant strains (6). Furthermore, MRSA is now spreading into the community. For example, in San Francisco, up to 50% of S. aureus cases found outside of hospitals have been forms of MRSA (6).

In 2002, strains of MRSA were also found to be resistant to the antibiotic vancomycin. Vancomycin, approved by the FDA in 1958, was considered to be the antibiotic of last resort when treating MRSA. The vancomycin-resistant strain of MRSA, called VRSA, had acquired resistance through horizontal gene transfer with the bacteria used to produce vancomycin (antibiotic-producing bacteria must be resistant to the drug that they are producing so that they are not susceptible to it) (6). Thus, the combination of the steadily increasing MRSA and the even more pernicious VRSA threat has stimulated research efforts to find ways to combat these new strains of disease-causing bacteria.

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Future avenues of research

Research targeted at discovering new antibiotic drugs has already found some success. In the past, antibiotic-producing bacteria were mainly found in soil sediment samples, but scientists are now looking in new locales to find different strains of bacteria. Searches in marine environments, such as the ocean floor, have been especially promising. At these depths, a bacterium that produces a new type of antifolate scaffold

was recently discovered. This scaffold could be used to prevent bacterial folic acid synthesis, - thus inhibiting the growth of bacteria (7). In addition, the sequencing of antibiotic-producing organisms like actinomycetes and mycobacteria has revealed that these organisms have the genetic information to code for over 25 different molecules with potential antibiotic properties, but are currently only known to manufacture 1 to 4 of such molecules molecules (7). Other projects have involved sequencing the genome of disease-causing bacteria in order to identify enzymes necessary for bacterial growth and then matching them with synthetic molecules that inhibit these enzymes. Another method is to screen whole libraries of existing compounds to see if they possess antibacterial capabilities. Recently, a group at Pfizer screened a library of molecules and found a group of pyridopyrimidines which showed antibacterial activity and also selected for bacteria over eukaryotic (animal) cells (7). Another research technique, used by Kosan, a biotech firm owned by Bristol-Meyers Squibb, is to manipulate the bacteria that are used to produce specific antibiotics. By altering the antibiotic-producing bacteria's enzymes, Kosan is able to manufacture antibiotics that differ only slightly from previous versions of the drug. However, such small changes in structure are enough for a drug to maintain potency against resistant strains of bacteria (2).

Early successes

Beyond these strategies, new drugs are already showing hope for providing solutions to antibiotic-resistant strains of bacteria. One such drug in development uses an innovative strategy to prevent natural selection, the underlying cause of resistance. Victor Nizet and Andrew Wang of the University of California, San Diego and Eric Oldfield of the University of Illinois used compounds which had previously been shown to have cholesterol-lowering effects (cholesterol biosynthesis inhibitors) to inhibit the synthesis of a pigment molecule that is part of S. aureus's disease-causing capability (8). This strategy renders the bacteria harmless without killing them. Thus, natural selection does not cause the propagation of resistant strains - limiting the ability of virulent strains to evolve.

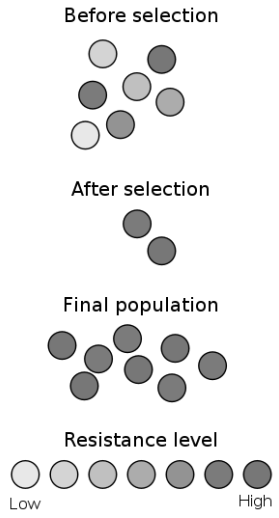

Figure 4: Nizet, Wang, and Oldfield's molecule, previously identified as a cholesterol biosynthesis inhibitor, would avoid this natural selection which causes the emergence of antibiotic resistant strains of bacteria.

Credit: Wikimedia Commons

Also, two drugs currently under development, platensimycin and platencin, show promise as candidates for a new class of antibiotics which target susceptibilities in bacteria that current drugs do not. Platensimycin, found in natural plant extracts, prevents phospholipid synthesis in bacteria by blocking FabF, an enzyme necessary for the production of bacterial fatty acids. Currently, the drug has had some success in treating MRSA and a vancomycin-resistant strain of Enterococcus (VRE) (5). The similarly structured drug, platencin, works effectively against a broader array of bacteria by targeting both the FabF and FabH enzymes in the fatty acid production pathway. Not only has this drug shown some success in treating MRSA and VRE, but platencin also has antibacterial activity against various other resistant strains of bacteria such as macrolide-resistant S. aureus and linezolid-resistant S. aureus (5). However, both platensimycin and platencin are far from being clinically available. Although they work *in vivo* when given by continuous infusion, they do not function as effectively when administered in periodic subcutaneous or oral doses (5). This ineffective functionality is attributed to their poor pharmacokinetic properties: the drugs have a weak ability to bind to their target. Researchers are now working on the design of these two molecules in order to improve this ability. These new drugs, in addition to the measured success of platensimycin and platencin at targeting new elements of disease-causing bacteria, provide some hope in the on-going fight against these pernicious pathogens. H

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—Seth Cassel '13 is a prospective Human Developmental and Regenerative Biology concentrator in Leverett House.

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