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# *The* Evolution *of* Antibiotics

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“The Lord hath created medicines out of the earth; and he that is wise will not abhor them” (Ecclesiastes 38:4).

During his search for such medicines, Selman A. Waksman, a biochemist and pioneer in soil microbiology, discovered streptomycin, neomycin, and many other antibiotics. Most of them were too weak to serve as therapeutic agents, or too toxic for human use. Waksman coined the term “antibiotics” to refer to a group of compounds produced by microorganisms which can inhibit the growth of other microorganisms, or even destroy them.

Today, antibiotics are the widely distributed “cure-all” for bacterial infections. Upon winning the Nobel Prize in 1952, Waksman predicted that future research would lead to the discovery of more active and less toxic agents and powerful combinations of antibiotic and synthetic compounds. We have witnessed the passing of his predictions and now envision the effect of warnings issued in his time; overuse and misuse of antibiotics have revealed adverse side effects and the development of drug-resistant strains.

#### HISTORY OF MICROBIAL THERAPY

Bacterial infections have afflicted civilizations for millennia. Tuberculosis was a major killer in ancient Egypt, *Yersinia pestis* resulted in the Black Death of medieval Europe, and Malaria, a bacterial disease, has been called one of the biggest killers in human history. During Christ’s ministry on earth, leprosy and certain venereal diseases were widespread as mentioned in the Bible (find biblical citation). Hippocrates wrote extensively on natural causes of disease, but generally ignored its transmission. In fact, it took more than 2000 years for medical science to develop an adequate theory regarding the spreading of disease.

Though causes of disease were not known, the use of molds and other crude materials to treat superficial infections can be traced back to at least 1500 B.C. through Egyptian papyri. It was not, however, until the late 19th century that the pioneering work of French chemist Louis Pasteur and German physician Robert Koch fully established the “germ theory” of disease, demonstrating that bacteria or other microbes were responsible for infectious diseases. By the end of the 1800s, virulent bacteria were recognized as a major contributor to disease. Preventive therapies were under development, many of them by Paul Ehrlich. Salvarsan, Erlich’s developed cure for syphilis, was used to treat the disease until World War II. Pasteur also noted that the growth of bacteria responsible for causing anthrax could be prevented by the presence of a contaminating fungus or mold; he suggested that this observation had therapeutic implications. This inhibition of growth of one organism by another was eventually

termed “antibiosis” by the French biologist Paul Vuillemin in 1890.

#### ALEXANDER FLEMING AND PENICILLIN

The antibiotic era truly began in 1928 with Alexander Fleming’s discovery of penicillin. Penicillin was, however, not the first antibiotic that he had discovered. Six years earlier, he discovered Lysozyme in tears and nasal secretions. He called the enzyme a “powerful antibacterial ferment” and part of a human’s natural defense.

Alexander Fleming graduated from St. Mary’s Medical School in London in 1908. As a member of the Royal Army Medical Corps during World War I, Fleming developed a keen interest in antibacterial agents. Attending to infected wounds, a common ailment during battles, he was convinced that the chemical antiseptics they utilized were more lethal to tissues than to invading bacteria. After the war, Fleming returned to his laboratory at St. Mary’s to continue his antimicrobial research.

The events that followed are considered the beginnings of penicillin. A spore of the mold *Penicillium notatum* entered his untidy laboratory through an open window and settled on a petri dish containing staphylococci bacteria. Upon returning from a vacation, Fleming discovered that all bacteria within the vicinity of the germinating spores were eradicated. Fleming pursued this observed method of antibiosis and discovered that even crude, dilute preparations of penicillin stopped the growth of bacteria, but it was essentially harmless to white blood cells.

It was not until World War II, however, that penicillin reached the mainstream of antimicrobial therapies. In

TABLE 1: MECHANISMS OF ACTION

- *Inhibition of cell wall synthesis*
- *Alteration of membrane integrity*
- *Inhibition of protein synthesis*
- *Inhibition of nucleic acid synthesis*

1945, Fleming, along with Howard Walter Florey and Ernst Boris Chain, received the Nobel Prize for physiology and chemistry for the discovery of penicillin. Further experiments proved that penicillin was active against staphylococcus, streptococcus, and several other pathogens. Research continued and by 1948, mass production of penicillin was underway at pharmaceutical plants throughout the world.

#### CURRENT ANTIBIOTIC THERAPIES

As more antimicrobial compounds and mechanisms have been elucidated, the arsenal of antibiotic therapies has grown substantially. This article will take a simplistic approach to the discussion of antibiotic mechanisms of action; the various families of antibiotics will be considered accordingly.

#### *Mechanisms of Action*

The task assigned to antibiotics is relatively straightforward: inhibit bacterial cells without altering human cells. To accomplish this function, antibiotics must take advantage of the dissimilarities between prokaryotic and eukaryotic cells. There are four general antibiotic mechanisms of action (*Table 1*). Each of them addresses a different structural or biochemical difference between cells.

A prokaryotic, or bacterial cell is a single-celled organism that lacks a well-defined nucleus and is enclosed by a membrane. The genetic material is a single strand of DNA and prokaryotes lack most organelles found in animal cells, including mitochondria. All bacteria are, however, surrounded by a rigid complex cell wall composed of peptidoglycan, and contain ribosomes which are distinctly smaller than those in higher organisms. Inhibition of the synthesis and growth of this cell wall stops bacterial growth at the cellular level. Many of the beta-lactam antibiotics, including pioneer penicillins and cephalosporins, suppress the growth of bacteria by destroying the proteoglycan cell wall.

The integrity of the bacterial membrane can be disrupted by agents that act directly upon the cell membrane. This interference alters the permeability of the membrane, leading to leakage of intracellular compounds. Polymyxin and Colistimethane fall into this category.

Another method of exploiting the differences between prokaryotes and eukaryotes is in the ribosomal structure. The subunits of ribosomes are larger in human cells than they are in bacteria. Thus, agents which alter or destroy the smaller 30 S or 50 S ribosomal subunits of bacteria will impede the production of bacterial proteins while leaving mammalian cells unaffected. Bacteria which are unable to produce proteins will die out swiftly. Chloramphenicol, the macrolides, the aminoglycosides, and the

**TABLE 2: SEVEN NEW CLASSES OF ANTIBIOTICS**

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- *Augmented penicillins*
  - *Carbapenems*
  - *Carbacephams*
  - *Monobactams*
  - *Thienamycins*
  - *Fluoroquinolones*
  - *Azilides*
- 

tetracyclines are examples of bacteriostatic drugs which inhibit bacterial protein synthesis; the mechanism will be discussed at length later in the article.

Finally, nucleic acid synthesis can be inhibited by antibiotic agents in two ways. Certain agents, such as the rifamycins, inhibit DNA dependent RNA Polymerase. Other drugs, such as the quinolone family, inhibit DNA gyrase, the enzyme that prevents excessive supercoiling during DNA replication and transcription. There is also the possibility that some antimicrobial compounds block bacterial conversion of Para-Amino Benzoic Acid (PABA) to tetrahydrofolate (THF), a necessary cofactor in DNA synthesis.

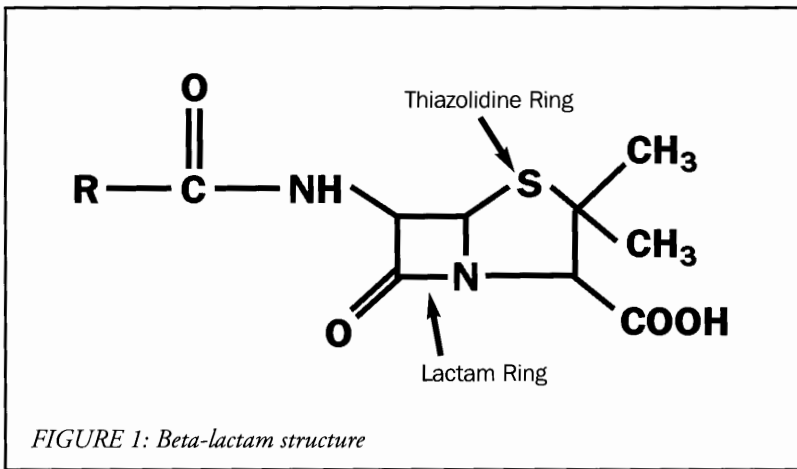
Presently, we are unaware of the precise mechanisms of all known antibacterial drugs; additional categories are likely to emerge as more complex mechanisms of action are determined.

#### ANTIBIOTIC FAMILIES

During the 1940s and 1950s, the golden age of antibiotics, many valuable antibiotics were discovered and purified. The discovery of novel agents, however, halted in 1960; most of the antibiotics introduced since are slight modifications of the original drugs. Modern antibiotics can be classified as either beta-lactam or non-beta-lactam molecules. Within each classification, there are various families which increase in size and number to keep up with demands placed on science by the earth's resilient bacteria. In addition to traditional antibiotics, the past eight years have introduced seven new classes of antibiotics (*Table 2*). Though based on their predecessors, these compounds bring new weapons to the arsenal of antibiotic therapies.

#### *Beta-Lactams*

Beta-lactam antibiotics comprise the pioneers and perhaps most important group of antibiotics. They include penicillins, cephalosporins, and several newer species. The mechanism of action for this class is inhibition of bacterial cell wall synthesis. Although several processes



may be responsible for this inhibition, interference with terminal peptidoglycan cross-linking is the most probable. This terminal event in bacterial cell wall formation is essential for many bacteria, but is primarily used to combat the gram positive species. There are currently more than 100 beta-lactam antibiotics in use today.

**Penicillins:** Although several other antimicrobial agents have been produced since penicillin became available, these are still widely used antibiotics. Penicillin G, the first antibiotic to come into broad use, remains one of the cheapest, safest, and most effective antibacterial treatments available. Penicillin V is similar in its activity to penicillin G, but because it is not destroyed by stomach acid it is the more commonly used oral form. Penicillins G and V are the drugs of choice for treating many gram-positive bacterial infections. Thus, they are still used to treat infections caused by gram-positive *Staphylococcus aureus*, *Streptococcus pyogenes* (strep throat), and *Streptococcus pneumoniae* (respiratory tract infections). These penicillins are also used to treat the sexually transmitted diseases gonorrhea and syphilis.

Methicillin was the first penicillin to have activity against the staphylococcal strains that were resistant to penicillin G. Other penicillins with similar activity are cloxacillin and dicloxacillin; they have the property of being orally active, unlike methicillin. Ampicillin and amoxicillin are similar antibiotics with a broader spectrum of activity than earlier penicillins, as they are active against common gram-negative bacteria as well as gram-positive bacteria. But they are not active against penicillin G resistant staphylococci. Both are effective on oral administration and are active against the gram-negative bacterium *Escherichia coli* (a common cause of urinary tract

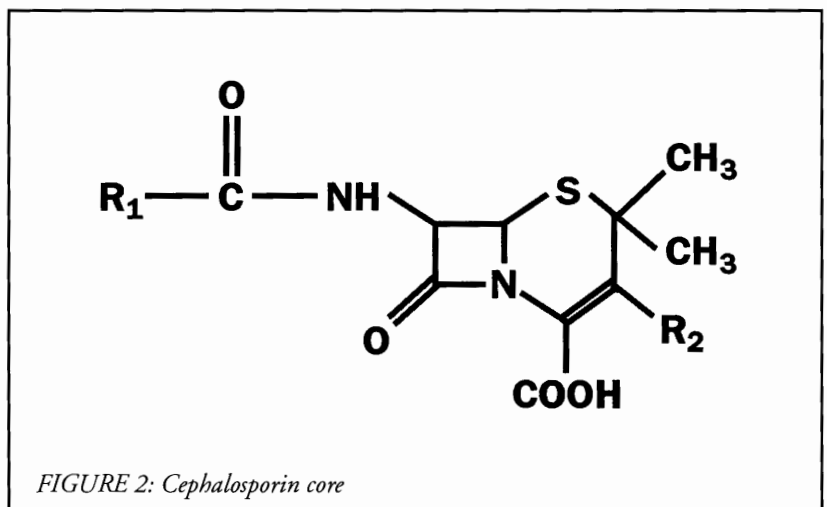
infections), *Haemophilus influenzae* (an important cause of ear infections and meningitis in infants), and *Salmonella typhi* (responsible for typhoid fever). Carbenicillin was the first penicillin synthesized to possess useful activity against *Pseudomonas aeruginosa*. This bacterium is normally only responsible for infections in hospitalized patients and had proved particularly difficult to treat. Although penicillins are extremely safe, patients can occasionally develop an immune reaction to them and become allergic. In such cases the availability of alternative antibiotics is critical.

A third category of penicillins encompass ampicillin, amoxicillin and bacampicillin. Their activity is extended to include *H. influenzae*, *E. coli*, and *P. mirabilis* which are not covered by the aforementioned categories.

**Cephalosporins:** Cephalosporins were initially isolated in 1948 when crude cultures of *Cephalosporium acremonium* was found to inhibit the in vitro growth of *Staph aureus* and to cure typhoid fever in humans. Once the antimicrobial compound was isolated, it became possible to produce synthetic compounds with activity much greater than the prototype substance.

The cephalosporin structure contains the basic beta-lactam ring and allows for more gram negative activity than the penicillins and aminocillins. Substitutions at the "R" sites allows for variation in the spectrum of activity and duration of antibiotic action.

Cephalosporins are grouped into three "generations" by their antimicrobial properties. The first cephalosporins were designated first-generation while later, more extended spectrum cephalosporins were classified as second generation cephalosporins. In addition to the current generations of cephalosporins, a fourth has been pro-



posed. Significantly, each newer generation of cephalosporins has greater gram negative antimicrobial properties than the preceding generation. Successive generations follow a trend of increased dosing frequencies and palatability. However, total daily doses remain fairly constant. Most second- and third-generation cephalosporins haven't been approved for use in patients less than six months of age

First-generation cephalosporins have activity against staphylococcus and streptococcus, along with Proteus, E. coli, and Klebsiella. Second-generation cephalosporins broaden the spectrum, including activity against H. influenza, while the third generations have greatly expanded gram negative coverage. First-generation cephalosporins are useful in treating skin and urinary infections; later generations are useful against systemic and respiratory infections

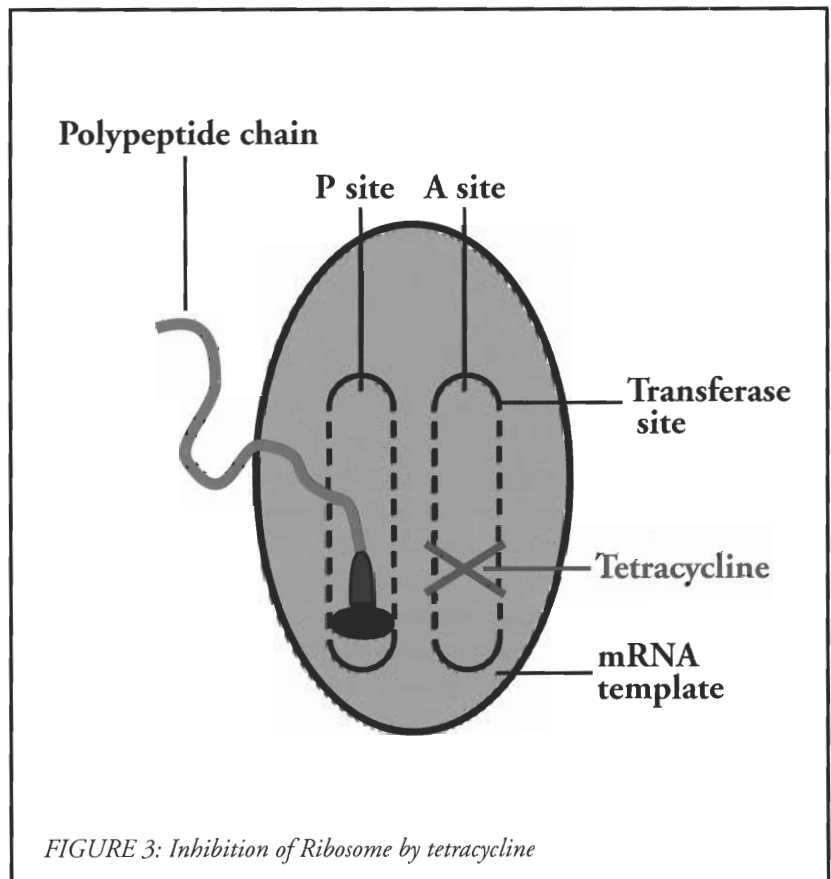
A fourth-generation cephalosporin is currently under development. These antimicrobials are projected to have an extended spectrum of activity for gram negative and gram positive organisms, minimal beta-lactamase activity due to rapid periplasmic penetration and high penicillin-binding protein (PBP) access, and a spectrum of activity which includes gram negative organisms with multiple drug resistance patterns (such as Enterobacter and Klebsiella). Cefepime (Maxipime) is one of these fourth generation cephalosporins. It is currently available in an injectable form for use in adults and children over 12 years old.

#### Non Beta-Lactam Antibiotics

Modern manifestations of respiratory diseases have brought a renewed interest to this class of antibiotics. Beta-lactam compounds are unable to concentrate in alveolar macrophages and there is a dramatically increased incidence of beta-lactamase producing pathogens. Vari-

**TABLE 3: NON-BETA-LACTAM ANTIBIOTICS**

- Aminoglycosides
- Quinolones
- Sulfonamides
- Macrolides
- Tetracyclines



*FIGURE 3: Inhibition of Ribosome by tetracycline*

ous other antimicrobials must thus come to the rescue.

The non beta-lactam antibiotics can be classed into five families (Table 3). Each has an independent structure and activity against certain pathogens.

**Aminoglycosides:** This group of compounds was initially discovered in the form of Streptomycin shortly after penicillin was released to the public. In 1944, Waksman was the first to show that the compound inhibits tubercle bacillus along with various gram-negative and gram-positive microorganisms. Aminoglycosides are used primarily in gram-negative aerobic bacteria and are potent inhibitors of protein synthesis. As their name implies, aminoglycosides contain amino sugars glycosidically linked to an aminocyclitol ring.

In addition to Streptomycin and Kanamycin, both derivatives of similar molds, the aminoglycosides include gentamicin, netilmicin and neomycin. The group inhibits protein synthesis by binding to prokaryotic ribosomal RNA at the site of the ribosomal decoding region (Alper, 98). This disrupts translation at the ribosome level and accounts for the rapid bacteriocidal effect of aminoglycosides.

Aminoglycosides diffuse through bacterial cell membranes through channels formed by porin proteins. Retarding this permeation is one way in which bacteria may become resistant to aminoglycosides. Resistance can

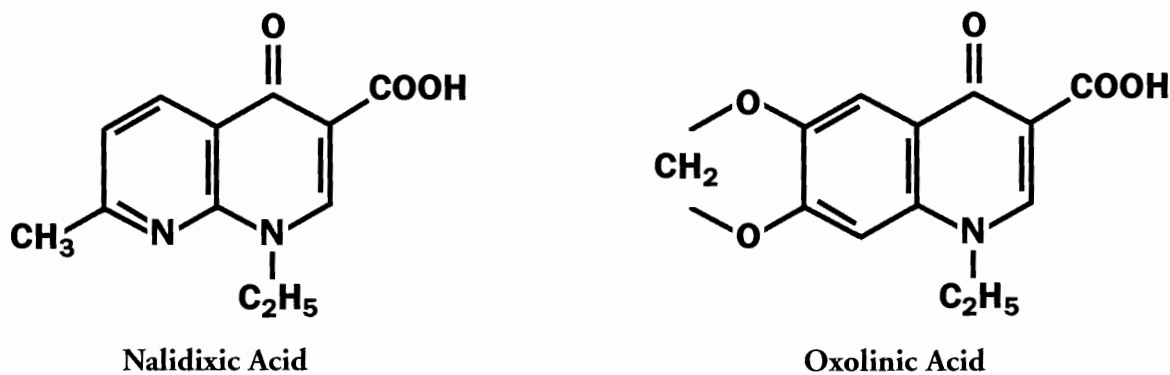


FIGURE 4: Structure of quinolones

also develop due to inactivation of the drug by bacterial enzymes or low affinity of the drug for ribosomal RNA. (Bryan 1988) The latter two processes are much more important clinically and may be overcome by combined administration with penicillin (Goodman).

**Sulfonamides:** This class of drugs was the first to be an effective chemotherapeutic agent in the prevention and cure of bacterial infections in humans. They were developed in the 1930s by German and English investigators. After the introduction of penicillin and subsequent antimicrobial agents, the usefulness of sulfonamides diminished and they now occupy a relatively small portion of a physician's antibiotic arsenal.

The sulfonamides are derivatives of para-aminobenzenesulfonamide and all have some resemblance to Para-aminobenzoic acid (PABA), the bacterial precursor of folic acid. Their mechanism of action is a competitive antagonism of PABA, preventing normal synthesis of folic acid. More specifically, the drugs inhibit dihydropteroate synthase, the enzyme responsible for folic acid synthesis. This mechanism limits sulfonamides to bacteriostatic action, and resistance develops commonly through mutations in dihydropteroate synthase, rendering sulfonamides useless. These mutations are generally persistent and irreversible (Triglia, 97).

The sulfonamides may be classified into three groups on the basis of the quickness with which they are absorbed and excreted. The first group, sulfasoxazole and sulfadiazene, are absorbed and excreted very rapidly. The second group, such as sulfasalazine, are absorbed very poorly and are thus active in the lumen of the intestines. Sulfacetamide, mafedine, and silver sulfadiazine are employed mainly for topical use and are members of a third group. The fourth group, which includes long-acting sulfadioxone, are absorbed rapidly but excreted slowly.

**Tetracyclines:** After the advent of penicillin, microbi-

ologists throughout the world systematically screened soil samples in the hope of discovering more antimicrobial agents. Chlortetracycline, the first of the tetracycline family, was discovered as a result of such investigations in 1948. Several tetracyclines have been developed since which have a broad range of activity against gram positive and gram negative bacteria of the aerobic and anaerobic variety.

Like aminoglycosides, the tetracyclines are thought to inhibit bacterial synthesis of proteins. They do so, however, by binding to the 30S ribosomal subunit, preventing access of transfer RNA to the acceptor site on the mRNA-ribosome complex (Goodman). They are effective against several bacteria which are resistant to the cell-wall-active antibiotics such as *Rickettsia*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, and some atypical mycobacteria. In addition to their antibacterial action, researchers now contend that tetracyclines might be of assistance in the treatment of arthritis, osteoporosis, and cancer, which are all characterized by the overproduction of tissue-degrading enzymes. Tetracyclines can inhibit the activity of these enzymes that break down connective tissue and bone (JADA, 97).

There are nearly a dozen modifications of the tetracycline molecule available as antibiotics. The agents available in the United States include tetracycline, oxytetracycline, demeclocycline, doxycycline, minocycline, and chlortetracycline. As they are all similar, they are all effective against a broad range of bacteria and when a microorganism becomes resistant to one tetracycline, it usually exhibits resistance to all of the others.

**Quinolones:** The earlier quinolones, developed in the early 1960s, consisted of nalidixic acid and its derivatives (see Figure 4). These drugs are of small significance now due to their poor pharmacokinetic activity and the rapid development of bacterial resistance. Later quinolones were based on oxilinic acid, a compound similar to

nalidixic acid, only less nitrogenous. More recently, the development of fluoridated versions of quinolones have come onto the scene. These agents, which will be discussed at length later, have improved therapeutic value, fewer side effects and less occurrence of microbial resistance.

The antimicrobial activity of the quinolones is based on their ability to inhibit DNA gyrase. DNA gyrase is a bacterial enzyme which prevents excessive supercoiling as DNA strands are separated during replication and transcription. The enzyme is not found in eukaryotes and mutations on the gene that encode the enzyme can occur resulting in resistance to quinolones and related agents.

**Macrolides:** In the early 1950s, researchers discovered a strain of *Streptomyces erythrus* that produced a potent antimicrobial substance. That substance, later named erythromycin, became the first of the macrolide class of antibiotics. Clairithromycin and Azithromycin, two semi-synthetic derivatives of erythromycin have since become popular. These orally active agents are all chemically similar, differing only in methyl substitutions within the lactone ring.

Renewed interest in the macrolides is due to the recent uprising in infections due to *Legionella*, *Mycoplasma* and *Chlamydia*. This class of antibiotics inhibits bacterial protein synthesis by binding reversibly to the 50S subunit of the prokaryotic ribosome. Though bacteriocidal at high levels, the macrolides are usually bacteriostatic against aerobic gram negative cocci and bacilli. It is generally believed that the macrolides inhibit the translocation step of translation rather than peptide bond formation (*Figure 5, next page*).

Resistance to macrolide antibiotics can occur with chromosomal mutations on DNA encoding the larger ribosomal subunit. Some micro-organisms may also produce esterase enzymes which inactivate macrolides and certain species of *Staph epidermidis* have developed alterations on the cell membrane which decrease its permeability to the macrolides.

In addition to the three infectious organisms mentioned above, the macrolides are also useful against *H. pylori*, Diphtheria, Pertussis, Tetanus, and several sexually transmitted diseases. The treatment of gastroenteritis caused by *Campylobacter jejuni* has also been successfully treated with macrolide antibiotics (Hoshino K, et al, 1998). Further uses for macrolides, especially azithromycin and clarithromycin are currently under investigation. Research suggests that macrolides improve clinical symptoms in adult AIDS patients and dramatically reduce infections by mycobacterium. The newer macrolides may effectively eradicate *H. pylori* related ulcers and make a dent in gastritis caused by the campylobacter species (Tarlow MJ 1997)

#### THE SEVEN NEW ANTIBIOTIC CLASSES

Due to the increasing prevalence of bacterial resistance to antimicrobial agents, medical research has continued to develop more effective antibiotics. The past decade has seen the introduction of a number of new potent antimicrobial agents, including broad-spectrum beta-lactam compounds such as third-generation cephalosporins, carbapenems, and monobactams; thienamycins, combinations of penicillins with inhibitors of beta-lactamase, and fluoroquinolones are also examples.

The seven "new" categories of antibiotics (see *Table 2*) do not differ widely from our arsenal of the past 30 years. They are primarily synthetic and significantly more effective in fighting bacteria. They are classed according to molecular structure and mechanism of antibiotic action. The first six mentioned in the figure are beta-lactam derivatives; the last one is a non-beta-lactam.

**Augmented penicillins:** Three molecules which are modifications of the penicillin have been developed. These compounds, developed to counteract the beta-lactamase enzyme produce by penicillin-resistant microbes, are beta-lactamase inhibitors; they bind beta-lactamase, allowing antibiotics to fulfill their purpose in the organism.

Clavulanic acid is a "suicide inhibitor" of beta-lactamase and is administered in conjunction with amoxicillin in an oral form called Augmentin. When the combination is given parenterally, it is called Timentin. Sulbactam and Tazobactam are two other beta-lactamase inhibitors. Both may be administered orally or parenterally with other beta-lactam antibiotics. The augmented penicillins are not effective against all penicillin-resistant bacteria.

**Carbapenems and Thienamycins:** These two groups deserve discussion together due to their chemical and antibiotic similarities. Both classes are beta-lactam compounds which disrupt cell wall synthesis and have high activity against streptococci, enterococci, staphylococci, and *Listeria*. Currently available carbapenems cannot be administered orally. The carbapenems can overcome resistance to many of the earlier beta-lactam drugs.

Carbapenems include Imipenem, which is also a thienamycin, and Meropenem. Imipenem is the most active agent currently available against many bacteria. It is marketed with cilastatin, a compound which inhibits imipenem degradation. The two are used together clinically against infections of the urinary and lower respiratory tracts (goodman). Meropenem has not received wide clinical attention. New carbapenems with increased activity against resistant microbes are currently under development, as are several with oral activity.

Imipenem differs chemically from penicillins and cephalosporins but has a similar mode of action. It is a potent antibacterial agent with a broad spectrum of activ-

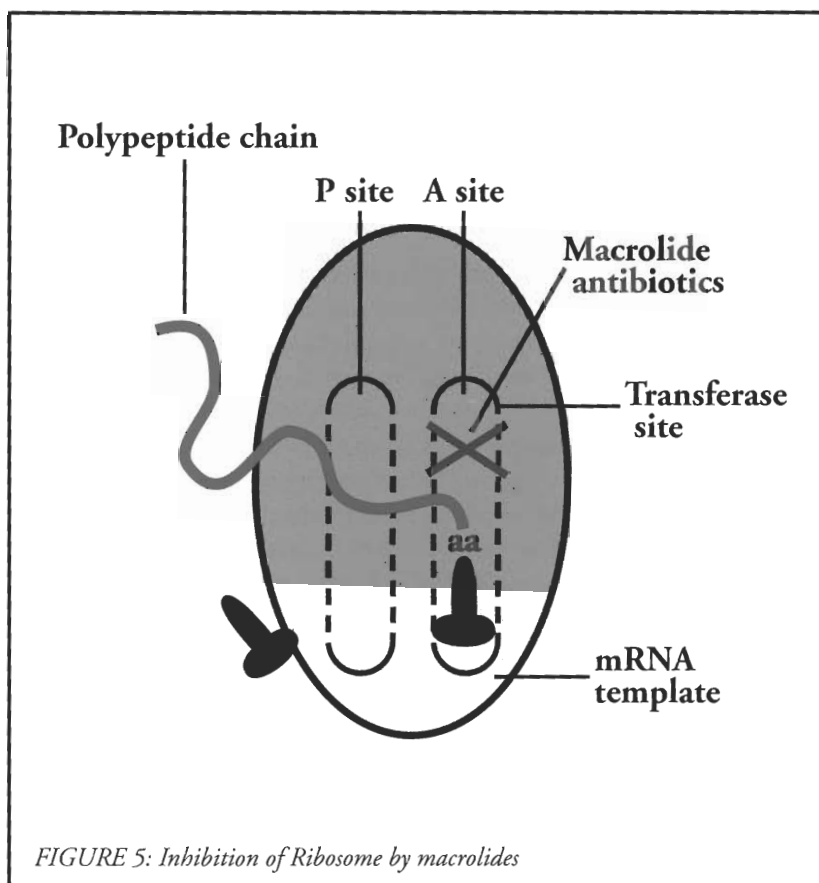


FIGURE 5: Inhibition of Ribosome by macrolides

ity encompassing both aerobes and anaerobes. It does not, however, offer a great improvement over other available agents for the treatment of infections caused by problem organisms such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* and enterococci. The results of clinical trials suggest that imipenem is efficacious and toxic side effects do not appear to be a problem (Williams 86).

**Carbacephams:** Research still required.

**Monobactams:** The monobactams display similar activity to carbapenems. When compared to other beta-lactams, certain species of monobactams display more activity against many species of the family Enterobacteriaceae (Fung 1997). Synergy between the monobactams and beta-lactamase-labile antibiotics were observed when such combinations were tested against strains of Enterobacteriaceae that produce large amounts of beta-lactamases (heinz).

The monobactams, which include tigemonam and aztreonam, have higher activity against gram negative species of bacteria than amoxicillin/clavulanic acid, aztreonam, and the third generation cephalosporins (Rylander, 88). Aztreonam exhibits effects more similar to aminoglycosides and appears to be effective in patients allergic to the penicillins.

**Fluoroquinolones:** As discussed previously, the fluo-

roquinolones are simply a fluoridated version of the quinolone molecule. These compounds, which include ciprofloxacin (cipro) and ofloxacin (Floxin), are as well tolerated as the quinolones but possess a much broader range of antimicrobial activity. A further advantage is that resistance does not occur readily against fluoroquinolones.

The fluoroquinolones are primarily useful against bacteria infecting the intestinal tract. These microorganisms include *E. coli* and various strains of *Salmonella*, *Shigella*, *Enterobacter*, *Campylobacter*, and *Neisseria*. (sanders, 88) Again, the mechanism of action for all quinolones is inhibition of DNA gyrase, a bacterial enzyme required for bacterial growth and proliferation.

A recently developed fluoroquinolone called Gatifloxacin has activity more potent than those of all other fluoroquinolones, against mutant strains of certain bacteria. This suggests that gatifloxacin possesses the most potent inhibitory activity, among the quinolones, against mutated DNA

gyrase which causes bacterial resistance. Gatifloxacin displays good activity against quinolone-resistant clinical isolates of *Staph aureus* harboring resistance-causing mutations (Fukuda).

#### BACTERIAL RESISTANCE

Bacteria become resistant to individual antibiotics through the development of specific defense mechanisms which render the antibiotic ineffective. Not all bacteria develop the same types of resistance. Generally, bacteria may become resistant to an antibiotic by utilizing one of three mechanisms: (1) Prevent the antibiotic from binding with and entering the organism at the cell wall or cell membrane level, (2) Produce an enzyme that inactivates the antibiotic (beta-lactamase enzymes in the case of bacteria resistant to penicillin, *H. influenza* and *M. catarrhalis*), and (3) Change the internal binding site of the antibiotic.

An example of the second type of resistance is the infamous beta-lactamase enzymes. There are actually dozens of enzymes, produced by many different bacteria, which are capable of degrading the beta-lactam structured antibiotics. Unfortunately, this form of antibiotic resistance can be transmitted to other bacteria. Perhaps even more significant is the emergence of penicillin resistant pneumococci (PRP). Since the late 1980's, PRP have been

## STEPS TO TAKE TO ELIMINATE RESISTANCE

- Wash your hands
- Immunize
- Stress compliance
- Educate and stay educated
- Know local resistance patterns
- Don't treat viral infections with antibiotics
- Use the most appropriate spectrum antibiotic for each infection (avoid "over-kill")
- Limit antimicrobial prophylaxis if possible
- Shorten the duration of antibiotic treatment if possible

Leiberman, J.M., 1994

reported with increasing frequency (over 20% in 1994). Unfortunately, many of the PRP are also resistant to other beta-lactam antibiotics, as well as sulfas. Thus, antibiotic resistance can be spread among bacteria.

The clinician plays a significant role in reducing the problem of antimicrobial resistance. Viral illness should not be treated with antibiotics and patients should be educated on compliance issues and use and misuse of antibiotics. It is crucial to stress patient compliance with timing and duration of antibiotic treatment. It is further important to prescribe the most appropriate antibiotic for each infection, avoiding overkill and prolonging the development of resistance to more powerful antibiotics.

## CONCLUSIONS

Dealing with microbial infections is an integral part of clinical practice. The vast number of antimicrobial agents available, including those new ones which are constantly being introduced, requires clinicians to keep abreast of the properties, antimicrobial activities, clinical uses and possible adverse effects of these agents. This article was simply an overview of the evolution of several classes of antimicrobial agents commonly used in daily practice, with the goal of leading medical clinicians toward rational and judicious usage of these potent medications.

Bacterial infections have plagued mankind for millennia. The future will likely introduce bacterial illnesses for which we do not currently have a cure. Antibiotic development is a race against deadly microorganisms, for which we must constantly prepare more diligently and slow our bacterial opponent as effectively as possible.

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