ANTIBIOTIC CLASSIFICATION A NEED TO UNDERSTAND

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PEER REVIEWED

Antibiotics are some of the most commonly used prescription medications in primary care. Drastic bacterial resistance against certain antibiotics has developed over the past few decades. This dilemma has originated in part from a general lack of understanding about the appropriate use of antibiotics. The less knowledge that health care providers and patients have about antibacterials, the more apt they are to misuse them. The ramifications of continued antibiotic misuse could include global bacterial resistance to a large number of these medications. Increased bacterial resistance will result in the inability to treat effectively numerous common primary care problems and potentially life-threatening diseases.[1]

A first step in decreasing antibiotic misuse is a better understanding of these drugs and the mechanisms by which they work. An appreciation for antibiotic classification and mechanism will allow clinicians to make educated decisions about antibiotic prescriptions. In addition, educating the public and health care providers has been shown to reverse resistance trends.[1]

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Classification

The classification of most antibiotics is based on mechanisms of action upon the bacterial cell. These actions are directed against the cell wall structure, cell membrane permeability, protein synthesis and nucleic acid synthesis.[2] In addition, all classes of antibiotics may be described as either bacteriostatic or bactericidal. Most antibiotics are considered bactericidal with the exception of macrolides, tetracyclines, chloramphenicol and sulfonamides, which inhibit bacterial growth until the body's own immune defenses can destroy the bacteria. Therefore, caution should be exercised when prescribing these latter classes of antibiotics to immunosuppressed patients.[3]

Drastic bacterial resistance against certain antibiotics has developed over the past few decades. This dilemma has originated in part from a general lack of understanding about the appropriate use of antibiotics.

The first mechanism of action that characterizes several classes of antibiotics is the destruction or the inhibition of the bacterial cell wall. The categories of antibiotics using this method of bacterial destruction include penicillins, cephalosporins, monobactams, vancomycin, bacitracin and carbapenems.[3,4]

Penicillins

Penicillins are one of the oldest classes of antibiotics. They are also known as beta-lactamase drugs because of the four-part lactam ring in their structure. Penicillins bind to specific proteins in the cell wall that are responsible for catalyzing certain chemical reactions that are essential for cell wall stabilization. Excretion of penicillins is mainly via the renal tubules and in part through bile.

Categorization of the penicillins is based on bacterial coverage. Penicillins include penicillin G, aminopenicillins, anti-staphylococcal (penicillinase-resistant) penicillins and anti-▶

pseudomonal penicillins.[4,5] Penicillin G is the first-line drug used for certain infections involving streptococci, meningococci, enterococci, non–beta-lactamase producing staphylococci, syphilis and anthrax. This antibacterial is available in intravenous form. Pen VK or Veetids may be used for minor infections. Intramuscular injections of penicillin work well in the treatment or prophylaxis of beta-hemolytic streptococcus pharyngitis or syphilis.[4]

Aminopenicillins have an extra side chain that allows easier penetration of Gram-negative organisms. These penicillins cover the same infections as penicillin G, plus some Gram-negative bacteria such as *Escherichia coli*, *Listeria monocytogenes* and shigella species. This subclass may also work against some anaerobes. However, these penicillins are ineffective against beta-lactamase–positive organisms such as *Moraxella catarrhalis* or *Haemophilus influenzae*. Aminopenicillins include ampicillin or amoxicillin. When combined with another agent, however, these penicillins can be effective against beta-lactamase–producing bacteria. One such combination is amoxicillin/clavulanate (Augmentin). Clinically, aminopenicillins may be effective in treating certain respiratory tract infections such as sinusitis, otitis or bronchitis.[3-5]

Another subclass of the penicillin antibiotics is the extended-spectrum anti-pseudomonal penicillins. This subgroup, like the aminopenicillins, works effectively against Gram-negative and Gram-positive bacteria. In addition, they exhibit anti-pseudomonal activity that the other penicillin groups lack. However, these anti-pseudomonal agents are ineffective against staphylococcal beta-lactamases unless used in combination with a beta-lactamase inhibitor. Examples of this subgroup include ticarcillin or piperacillin. Some combination anti-pseudomonals with beta-lactamase inhibitors include piperacillin/tazobactam (Zosyn) and ticarcillin/clavulanate (Timentin).[3-5] These penicillins are available in IV form for many skin and soft-tissue infections, lower respiratory-tract infections, bone and joint infections, urinary tract infections and gynecologic and intra-abdominal infections.[6]

The remaining subclass of penicillins is the penicillinase-resistant group. Compared with other penicillins, this group has a narrow spectrum of antibacterial activity. This category of penicillin works effectively against most Gram-positive staphylococci and some streptococci. However, these penicillins have no action against Gram-negative organisms, Gram-positive enterococci or methicillin-resistant *Staphylococcus aureus* (MRSA). Examples of this penicillinase group include methicillin, nafcillin, oxacillin, cloxacillin and dicloxacillin. Mild nonsystemic staphylococcal infections may be treated with oral oxacillin, cloxacillin or dicloxacillin. More serious infections require IV oxacillin or nafcillin.[4]

Cephalosporins

The second class of antibiotics utilizing bacterial cell wall destruction is the cephalosporins. These antibiotics bear similarities to the penicillins in configuration, in mechanism of action and in method of excretion from the body. Cephalosporins are slightly more stable than penicillins and in many cases have a broader bacterial coverage. However, cephalosporins have limited activity against enterococci, MRSA, and *L. monocytogenes*.[3-5] The four subclasses of cephalosporins are labeled first-, second-, third- and fourth-generation cephalosporins.

First-generation cephalosporins are extremely active against Gram-positive cocci and many Gram-negative bacteria, excluding *Pseudomonas aeruginosa* and some proteus and enterobacter species. They also exert some action against certain types of anaerobic cocci. This subgroup is often administered for surgical prophylaxis and in the treatment of staphylococcal or streptococcal skin and soft-tissue infections. Some examples of commonly used first-generation cephalosporins include cefazolin (Ancef), available in IM or IV forms, and cephalexin (Keflex), available in oral form.[3-5]

Second-generation cephalosporins are slightly less active against Gram-positives and have better coverage against Gram-negative and some anaerobic organisms. Certain second-generations such as cefaclor, cefuroxime (Zinacef) and loracarbef (Lorabid) can be given orally to act against *H. influenzae* and *M. catarrhalis*. These drugs can be used to treat sinusitis, otitis, pharyngitis and respiratory tract infections. Other second-generations such as cefoxitin, cefotetan (Cefotan) and cefmetazole are available in IV form and have strong coverage against anaerobes. These cephalosporins are often utilized in gynecologic or abdominal infections such as peritonitis or diverticulitis.[3-5]

Third-generation cephalosporins have slightly less Gram-positive activity and greater Gram-negative coverage than the first or second generations. These antibiotics are reserved for serious infections such as meningitis, Lyme disease and gonorrhea. Examples include ceftazidime, which is available in IV form, and ceftriaxone (Rocephin) or cefotaxine (Claforan), which are available in IV or IM forms. Fourth-generation cephalosporins such as cefepime (Maxipime) are similar to the third-generations but are slightly more stable.[3-5]

Vancomycin, Bacitracin, Carbapenems

The other types of antibiotics that inhibit or destroy bacterial cell wall function include vancomycin, bacitracin and the carbapenems. Vancomycin has good antibacterial coverage against most Gram-positive bacteria. Vancomycin is usually administered IV but may be given orally for treatment of pseudomembranous colitis. The IV form of this drug is reserved for serious infections resistant to other antibiotics. These include infections involving MRSA, sepsis and endocarditis.[3-5] Bacitracin has good coverage against Gram-positives, treponema and neisseria strains. This antibiotic has little activity against Gram-negatives or anaerobes.

Because of its nephrotoxicity, bacitracin is primarily topical for surface wounds or lesions.[3-5]

The carbapenems are structurally similar to the penicillins and cephalosporins. This class includes imipenem and meropenem. Both antibiotics are administered IV for infections resistant to other antibiotics. They are broad-spectrum antibacterials with activity against Gram-positives, Gram-negatives and anaerobes.[4,7-11]

Polymyxins

The second method of bacterial destruction utilized by antibiotics involves alterations of cell-membrane permeability. The class of antibiotics that use this method is the polymyxins; polymyxin B is the main antibiotic in this category. This antibacterial is effective against many Gram-negative rods. Polymyxin B is available in topical form and is primarily used for superficial skin lacerations.[7]

The third mechanism of action commonly used by several classes of antibiotics involve inhibition of bacterial protein synthesis. These antibiotic groups include tetracyclines, macrolides and aminoglycosides, among others.

Tetracyclines

Tetracyclines are a large group of antibiotics that are bacteriostatic against a wide range of Gram-positive, Gram-negative and anaerobic bacteria. These antimicrobials bind to the 30S ribosomal subunit to prevent bacterial amino acid elongation. This class is excreted primarily via the kidney.

Tetracyclines are often drugs of choice when treating infections involving *Mycoplasma pneumoniae*, rickettsiae and chlamydia. They may be used in combination therapy to treat some gastric or duodenal infections by *Helicobacter pylori*.

Other indications may include acne, bronchitis exacerbations, urinary tract infections, community-acquired pneumonia and Lyme disease. Some tetracyclines are available in oral or IV form. These include doxycycline and minocycline. Others such as oxytetracycline and tetracycline are available as oral formulations.[3,5,6,8]

Macrolides, Aminoglycosides

Macrolides are another major class of antibiotics with bacteriostatic capabilities. This class binds to the 50S bacterial ribosomal subunit to inhibit microbial protein synthesis. Excretion occurs primarily via bile. These drugs have adequate coverage against streptococci, staphylococci and some Gram-negatives such as *Neisseria gonorrhoeae, H. influenzae* and chlamydia. These antibiotics offer little anaerobic coverage. Macrolides provide treatment of pneumonia, pertussis, upper respiratory tract infections, bronchitis, sinus infections and prophylaxis in some HIV-positive patients. Commonly used macrolides may be available in oral or IV forms. These may include erythromycin and clindamycin (Cleocin). Other macrolides prescribed as oral formulations may comprise of azithromycin (Zithromax) and clarithromycin (Biaxin).[3,5,6,8]

Another major class of bacterial protein synthesis inhibitors is the aminoglycosides. This group of antibiotics binds to the 30S bacterial ribosomal subunit to inhibit protein production. These antibacterials are excreted by the kidneys and are ototoxic and nephrotoxic. Aminoglycosides are active against staphylococci and Gram-negative aerobes such as *P. aeruginosa*. These drugs do not have anaerobic coverage. Aminoglycosides are primarily used for Gram-negative bacteremia or in combination treatment for endocarditis or tuberculosis. Examples include amikacin, streptomycin, tobramycin (Tobrex), gentamicin (Garamycin) and neomycin. Many of these antibiotics are available in IV or IM form.[3,5,9]

Other bacterial protein synthesis inhibitors include quinupristin/dalfopristin and chloramphenicol. Quinupristin/dalfopristin is active against Gram-positive bacteria and is used to treat vancomycin-resistant enterococci (VRE) and MRSA infections. Chloramphenicol binds to the 50S bacterial subunits to inhibit bacterial protein synthesis. This antibiotic is bacteriostatic against certain Gram-positive, Gram-negative and anaerobic organisms. This drug is reserved for serious infections such as typhoid fever, meningitis, rickettsial or *Bacteroides fragilis* infections, epiglottitis and some central nervous system abscesses.[3,5]

Lincosamines, Rifampin

Another type of bacterial protein synthesis inhibitors includes the lincosamines and rifampin. The lincosamines prevent protein formation via binding to the 50S bacterial ribosomal subunit. The most commonly used lincosamine is clindamycin. This class of antibiotics has good coverage against many Gram-positives and anaerobes but with little Gram-negative coverage. This antibiotic is clinically indicated to treat anaerobic infections such as intra-abdominal puncture wounds, pelvic abscesses and aspiration pneumonia.[3]

Rifampin blocks protein synthesis by binding to DNA-dependent RNA polymerase to block RNA transcription and resultant protein formation. This antibiotic has broad-spectrum activity, but its use is restricted by increased numbers of resistant strains. Rifampin is primarily used for the treatment of tuberculosis and leprosy.[3,5,11]

Quinolones and Sulfas

The last common mechanism of action utilized by some antibiotics is blockade of bacterial replication. Groups of antibiotics utilizing this mechanism of action include the fluoroquinolones, sulfa drugs, metronidazole and nitrofurantoin.

Fluoroquinolones are bactericidal antimicrobials that prevent the action of DNA gyrase, an essential enzyme of bacterial reproduction. These antibiotics are excreted via the kidney. This group of antimicrobials provides broad-spectrum coverage against Gram-negatives, and newer agents in the class have good Gram-positive coverage. This broad-spectrum coverage includes *E. coli*, shigella, salmonella, *S. pneumoniae, H. influenzae* and pseudomonas species, with little activity against anaerobes. These antibiotics are effective against a variety of conditions such as strep throat, pneumonia, urinary tract infections, sexually transmitted diseases, infectious diarrhea and intra-abdominal infections. Most fluoroquinolones are available in oral form. Commonly used fluoroquinolones include ciprofloxacin (Cipro), levofloxacin (Levaquin), norfloxacin, ofloxacin and trovafloxacin.[3,5,10]

The second group of antibiotics involved in the inhibition of the bacterial replication process is the sulfa drugs. These antibiotics inhibit a step in the production of folic acid, an essential component of nucleic acid synthesis. These drugs, like the fluoroquinolones, have broad-spectrum activity. However, many strains become easily resistant to the sulfa drugs and are thus often used in combination form. The most common uses for noncombination sulfas are in the treatment of bacterial conjunctivitis or urinary tract

infections. Combination forms may be used to treat toxoplasmosis, ulcerative colitis, burns and urinary tract infections and as rheumatic fever prophylaxis. Examples of frequently used sulfa drug combinations include erythromycin/sulfisoxazole (Pediazole) and trimethoprim-sulfamethoxazole (TMP-SMX). Pediazole is often utilized in the treatment of otitis media. TMP-SMX may be used to treat urinary tract infections, typhoid fever, otitis media, shigellosis, enterotoxigenic *E. coli* diarrhea and *Pneumocystis carinii* pneumonia.[3,5,6,10] Trimethoprim can be used by itself for certain infections.

Metronidazole and Nitrofurantoin

Two other antibiotics involved with the inhibition of bacterial replication are metronidazole and nitrofurantoin. Metronidazole is essential to inhibition of anaerobes and protozoa. This antimicrobial is reduced to a substance that interferes with the helical DNA structures of the anaerobes. It is ineffective against aerobic bacteria. Common indications for this drug include various protozoan infections, bacterial vaginosis, intra-abdominal infections, pelvic infections, *Clostridium difficile* colitis and anaerobic strains responsible for meningitis, brain abscesses or endocarditis.[3,5]

Nitrofurantoin is involved in the inhibition of several bacterial systems, including the direct destruction of bacterial DNA. Primary indications for this antibiotic are for urinary tract infections. This antimicrobial is effective against several Gram-positive and Gram-negative organisms such as *E. coli*, klebsiella, staphylococci and enterococci.[7]

Proper Use Is Key

Each type of antibiotic is categorized by one of four mechanisms of action. Clinicians must be aware of the various classes and mechanisms of action of these commonly prescribed drugs in order to gain a better appreciation for proper use of the common antibiotics. In doing so, clinicians will be in a better position to prescribe appropriate effective antibiotics, educate the public regarding proper antibiotic usage and help decrease emerging bacterial resistance to these antibiotics.

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References

1. Steinberg I. Clinical choices of antibiotics: judging judicious use. *Am J Manag Care.* 2000;6(23 suppl):S1178-S1188.

2. Antibacterials. ALtrius Biomedical Network Web page. Available at: http://www.anti-biotic.com/antibact.html. Accessed July 1, 2003.

3. Clinical Antibiotic Tutorial Site. McGill Medical Informatics. May 17, 1999. Available at: http://sprojects.mmi.mcgill.ca/antibiotic/. Accessed July 1, 2003.

4. Chambers HF. Beta-lactam antibiotics and other inhibitors of cell wall synthesis. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:754-773.

5. Antibacterial drugs. In: Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy.* 17th ed. Whitehouse Station, NJ: Merck Research Laboratories; 1999:1101-1127.

6. Infections and infestations. Antibiotics and antibacterials. In: *Monthly Prescribing Reference.* New York, NY: Prescribing Reference Inc; April 2001:181-199.

7. Chambers HF. Miscellaneous antimicrobial agents; disinfectants, antiseptics, and sterilants. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:845-853.

8. Chambers HF. Chloramphenicol, tetracyclines, macrolides, clindamycin, and streptogramins. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:774-783.

9. Chambers HF. Aminoglycosides and spectinomycin. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:784-792.

10. Chambers HF. Sulfonamides, trimethoprim, and quinolones. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:793-802.

11. Chambers HF. Antimycobacterial drugs. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 8th ed. New York, NY: McGraw Hill; 2000:803-813.