Paparella: Volume I: Basic Sciences and Related Disciplines

Section 6: Pharmacology

Chapter 28: Antibiotics

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The history of antibiotics goes back many centuries. The Chinese knew of the therapeutic utility of applying moldy soybean curd to skin infections over 2.500 years ago (Sande and Mandell, 1985). Pasteur and Joubert (1877) reported that anthrax bacilli could be administered to an animal in large numbers without causing illness if the other bacteria were co-administered. The modern age of chemotherapy of infectious disease began with the use of sulfanilamide in 1936 and accelerated with the introductions of penicillin in mass quantities in 1941. Further momentum was brought about by the discovery of streptomycin in 1944. The search for nontoxic, highly effective antimicrobial agents continues.

Antibiotics are chemical substances produced by living organisms (bacteria, fungi, or actinomycetes) that inhibit the growth of other microorganisms and may eventually kill these other organisms. A number of naturally-occurring substances have been modified chemically, creating the so-called semisynthetic antibiotics, which behave as prodrugs or which have enhanced therapeutic to toxic ratios. Finally, some substances such as isoniazid or ethambutol are completely synthetic and are useful in the treatment of tuberculosis (Sande and Mandell, 1985).

The choice of a drug for treating an infection depends on a number of factors. One such factor involves the activity of the drug against the pathogenic organism. Other factors include the intrinsic toxicity of the drug and the patient's clinical status such as the presence of renal failure, allergies, or pregnancy. Another consideration may involve cost when other factors are nearly equal.

Sulfonamides and Trimethoprim-Sulfamethoxazole

Sulfonamides

The sulfonamides were the initial chemotherapeutic agents to be used systematically to treat bacterial infections in humans. The name sulfonamide includes a series of synthetic derivatives of sulfanilamide. Sulfonamides exhibit a broad range of antimicrobial activity against both gram-positive and gram-negative organisms. The sulfonamides exert mainly a bacteriostatic action. These agents are active against group A *Streptococcus pyogenes, S. pneumoniae,* some strains of *Bacillus anthracis* and *Corynebacterium pneumoniae, Haemophilus influenzae* and *H. ducreyi, Brucella, Vibrio cholerae, Yersinia pestis, Nocardia, Actinomyces, Calymmatobacterium granulomatis,* and the agents responsible for trachoma, lymphogranuloma venereum, and inclusion conjunctivitis (Sande and Mandell, 1985). Sulfonamides are not longer used for gonorrhea because of the emergence of resistant strains. Many strains of *Neisseria meningitidis* and *Shigella* are resistant to the sulfonamides. Some strains of *Escherichia coli* isolated from patients with urinary tract infections are sensitive to sulfonamides. Other enteric bacteria tend to be resistant in vivo, although they are sensitive

in vitro.

The mechanism of action of sulfonamides is thought to involve the competitive antagonism of para-amino-benzoic acid (PABA) utilization by bacteria. Sulfonamides appear to prevent bacteria from incorporating PABA into the folic acid molecule. Thus, bacteria that do not require folic acid or that can utilize preformed folic acid are not affected. The bacteriostatic action of sulfonamides is competitively antagonized by PABA. Trimethoprim exerts a supra-additive effect in combination with a sulfonamide. Certain sulfonamides such as sulfasalazine are designed for local effects in the bowel, such as in the treatment of ulcerative colitis and regional enteritis. This drug is poorly absorbed from the gastrointestinal tract. The other sulfonamides are rapidly absorbed from the gastrointestinal tract. Subcutaneous injection of sodium salts of sulfonamides results in antibacterial levels in the blood. After systemic administration of adequate doses, the sulfonamides reach cerebrospinal fluid concentrations that are effective in meningitis. The sulfonamides are acetylated and oxidized primarily in the liver. The acetylated forms of some of the older sulfonamides are less soluble and contribute to crystalluria and renal complications. Most of the excretion of sulfonamides occurs in the urine by glomerular filtration. The sulfonamides can be divided into three groups: (1) agents that are rapidly absorbed and excreted, such as sulfisoxazole; (2) agents very poorly absorbed orally which are active in the bowel lumen, such as sulfasalazine; and (3) sulfonamides used mainly for topical use, such as sulfacetamide, mafenide, and silver sulfadiazine.

The recommended daily oral dose of sulfisoxazole for children is 120-150 mg/kg of body weight; one-half of this dose is given as a loading dose, followed by one-sixth of the daily dose every 4 hours but not exceeding 6 grams in 24 hours. For adults, the oral dose is 2 to 4 gm initially, followed by 1 gm every 4 to 6 hours.

Sulfisoxazole is highly soluble in urine compared with the older sulfonamides. Therefore, sulfisoxazole only infrequently causes hematuria or crystalluria (0.2 to 0.3 per cent), and the risk of anuria is very small. However, it is recommended that patients taking this drug ingest an adequate amount of water. Sulfisoxazole and all absorbable sulfonamides must be used with caution in patients with impaired renal function. All sulfonamides may produce potentially fatal hypersensitivity reactions.

Sulfamethoxazole is a compound that is structurally related to sulfisoxazole, but its rate of oral absorption and urinary excretion are slower. Precautions must be used to prevent crystalluria because of the acetylated rather insoluble metabolite in the urine. The dosage schedules for children are: 50 to 60 mg/kg initially, followed by 25 to 30 mg/kg in the morning and the evening. The dosage for adults with mild infections is 2.0 gm, followed by 1.0 gm every hours; for severe infections, the maintenance dose (1 gm) is given every 8 hours.

Sulfacetamide is a very soluble sulfonamide used topically for ophthalmic infections. Very high aqueous concentrations are nonirritating to the eye and yet are effectively bactericidal. This drug should not be used in patients allergic to sulfonamides. The initial dose of sodium sulfacetamide solution is one or two drops of 10 to 30 per cent solution applied topically to the eye every 2 hours for severe infections, and 3 to 4 times a day for chronic conditions. An ophthalmic ointment is also available.

Sulfasalazine is used in ulcerative colitis and regional enteritis.

Mafenide cream is used as a topical preparation for the prevention of infection of burns by a wide variety of gram-negative and gram-positive bacteria. It appears to be highly active in inhibiting the implantation of *Pseudomonas aeruginosa* but should not be used for established infection. There is rapid systemic absorption of mafenide. Adverse reactions include pain on application, allergic reactions, and loss of fluid by evaporation since occlusive dressings are not used. The drug inhibits carbonic anhydrase; the urine becomes alkaline, and metabolic acidosis may occur. Compensatory tachypnea with hyperventilation resulting in respiratory alkalosis can also occur.

Silver sulfadiazine is also used extensively for topical therapy of burns. Silver is slowly released and is toxic to microorganisms. This drug prevents invasion and can also eradicate *P. aeruginosa* and other sensitive microorganisms from burns.

Also, sulfonamides are potentially dangerous drugs. The overall incidence of reactions is about 5 per cent. Certain untoward effects preclude the subsequent use of these agents: drug fever and reaction involving the blood, bone marrow, kidney, liver, skin and peripheral nerves (Sande and Mandell, 1985).

Hematopoietic side effects include acute hemolytic anemia, agranulocytosis, thrombocytopenia, aplastic anemia (extremely rare), and eosinophilia. Renal side effects include crystalluria, toxic nephrosis, and hypersensitivity nephritis. The risk of crystalluria is reduced by large urine volume brought about by high fluid intake. Alkaline therapy can be used if urine pH is low.

Hypersensitivity reactions include vascular lesions, which may resemble polyarteritis nodosa; skin and mucous membrane manifestations (Stevens-Johnson syndrome), serum sickness, anaphylactoid reactions and drug fever. Liver damage may occur rarely. Other reactions include goiter, hypothyroidism, arthritis, neuropsychiatric disturbances, peripheral neuritis (very rare), anorexia, nausea, and vomiting. Premature babies may develop kernicterus because of displacement of bilirubin from plasma protein binding sites. Enzymes that acetylate sulfonamides are poorly developed in newborns.

Trimethoprim-Sulfamethoxazole

The combination of trimethoprim-sulfamethoxazole has been used extensively since 1968, mainly for the treatment of gram-negative infections. The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole, although the trimethoprim drug is 20 to 100 times more potent than the sulfamethoxazole (Sande and Mandell, 1985). The combination is active against most gram-positive and gram-negative bacteria but resistance may develop. Resistant organisms include *P. aeruginosa*, enterococci, and *Bacteroides fragilis.*

Trimethoprim-sulfamethoxazole is a bacteriostatic combination; however, bactericidal activity may be found against some microorganisms. This combination works by acting on two levels in the pathway for the synthesis of tetrahydrofolic acid in bacteria. The sulfonamide inhibits the incorporation of PABA into folate, and trimethoprim blocks the

reduction of dihydrofolate to tetrahydrofolate (Sande and Mandell, 1985). The optimal ratio for synergism of these two agents against most bacteria is 20 parts of sulfamethoxazole to one part of trimethoprim.

The pharmacokinetic profiles of the combination are designed to achieve a constant ratio of 20 to one. The half-lives of trimethoprim and sulfamethoxazole are about 11 and 10 hours, respectively. The recommended daily dose for children for treatment of urinary tract infections and otitis media is 8 mg/kg of trimethoprim and 40 mg/kg of sulfamethoxazole, given in two divided doses every 12 hours for 10 days. The combination should not be used in infants under 2 months of age, during pregnancy (at term), and in nursing mothers.

The usual adult dose is 800 mg of sulfamethoxazole plus 160 mg of trimethoprim every 12 hours for 10-14 days.

Little toxicity has been observed in the routine use of trimethoprim-sulfamethoxazole. The most common side effects involve the skin. However, severe cutaneous toxicity such as exfoliative dermatitis, Stevens-Johnson syndrome, or toxic epidermal necrolysis is rare. Nausea, vomiting, diarrhea, glossitis, and stomatitis are relatively common. Allergic cholestatic jaundice may be mild and transient. Headache, depression, or hallucinations may occur. A variety of anemias may be induced, especially in folate deficient patients. Aplastic, hemolytic, or macrocytic anemia may occur. Coagulation disorders, granulocytopenia, agranulocytosis, purpura, Henoch-Schoenlein purpura, and sulfhemoglobinemia have been reported. Permanent renal disease may follow the use of the combination in patients with renal disease (Sande and Mandell, 1985).

Therapeutic indications include urinary tract infections, acute exacerbations of chronic bronchitis, acute otitis media, and acute maxillary sinusitis. Trimethoprim-sulfamethoxazole should not be used to treat streptococcal pharyngitis, since it does not eliminate the organism. It may be used to treat shigellosis, and typhoid fever, to eradicate salmonella carrier states and to treat acute diarrhea caused by enteropathogenic *E. coli. Pneumocystis carinii* infection in immunosuppressed host, such as AIDS patients, is effectively treated by high-dose therapy. Acute gonorrheal urethritis, chancroid, and *Nocardia* and *Brucella* infections, respond to therapy with sulfamethoxazole-trimethoprim.

Beta-Lactam Antibiotics

This large group of antibiotics includes the penicillins, cephalosporins, and two new classes of antibiotics, the carbapenems and the monobactams. This class of antibiotics inhibits steps in bacterial cell wall synthesis or maintenance. More recent research has revealed that penicillins bind to specific proteins located between the cytoplasmic membrane and cell wall of bacteria. These penicillin-binding proteins play a critical role in maintaining the structure of the bacterial cell wall (Curtis, 1981). A series of penicillin-binding proteins have been identified and classified according to their molecular weight (Eng, 1984). Six difference beta-lactamases produced by bacteria have been identified. Some of these enzymes are penicillinases, some of which have activity against oxacillin. Others are cephalosporinases. Some bacteria may resist beta-lactam antibiotic action because of the inability of the antibiotic to penetrate the gram-negative cell wall (Eng, 1984). Therefore, the susceptibility of bacteria to a beta-lactam antibiotic depends on three factors: (1) the stability of the antibiotic to

enzymatic breakdown; (2) the ability of the antibiotic to penetrate the cell wall in order to reach the site of action (periplasmic space); and (3) the ability of the antibiotic to bind to various penicillin-binding proteins (Eng, 1984).

The series of antibiotics in the penicillin and cephalosporin categories of beta-lactam antibiotics have been clustered into various "generations" of compounds with similar properties within a given generation. Succeeding generations have indicated new series of compounds with new properties and a new antimicrobial spectrum of activity. Four generations of penicillins and three generations of cephalosporins have been described.

Penicillins

The discovery of penicillin and the determination of its spectrum of action and chemistry opened up a new era of antimicrobial therapy. In the 1950s, penicillin was successfully employed to treat infections caused by streptococci, staphylococci, *Neisseria,* and pneumococci. It soon became obvious that penicillin G lacked certain desirable qualities. Unaltered penicillin is rapidly excreted by the kidneys. This problem requires frequent dosing of the drug to maintain proper blood and tissue levels. Penicillin G is susceptible to inactivation by beta-lactamases, and is inactive against gram-negative rods, because of its inability to penetrate the cell wall to reach the site of action (Izaki et al, 1966). These limitations to the action of penicillin G led to the development of new generations of penicillins with extended spectrums of action. The penicillinase-resistant group of penicillins (methicillin, nafcillin, oxacillin, cloxacillin, and dicloxacillin) are generally less active than penicillin G, but their stability to the action of penicillinases makes them useful for the treatment of infections caused by *Staphylococcus aureus.* However, infections due to methicillin-resistant *S. aureus* are of increasing importance in the United States. Strains of methicillin-resistant *S. aureus* are also resistant to all penicillins; however, vancomycin is effective against all strains of methicillin-resistant *S. aureus* (Watanakunakorn, 1982). Methicillin resistance is not caused by enzymatic inactivation. It is intrinsic, chromosomally mediated, and heterogeneous. Methicillin resistance is related to decreased affinity of the penicillin-binding proteins in the cell wall for methicillin (Eng, 1984).

The second generation penicillins include the ampicillins (ampicillin, amoxicillin, hetacillin, cyclacillin and bacampicillin). These compounds have chemical properties that allow penetration of the cell wall of enteric gram-negative rods and *H. influenzae.* Amoxicillin has the identical antimicrobial spectrum to that of ampicillin, but amoxicillin has a longer serum half-life and increased absorption from the gastrointestinal tract, thereby resulting in a lower incidence of diarrhea (Neu, 1974). These drugs are susceptible to hydrolysis by beta-lactamases produced by a number of *H. influenzae* strains as well as *Klebsiella pneumoniae.* To combat the beta-lactamase produced by *H. influenzae* and *Klebsiella pneumoniae,* clavulanic acid has been added to amoxicillin (Neu and Fu, 1978). Clavulanic acid is a natural product of *S. clavuligenes* and has a structure similar to penicillin. Although this compound has little intrinsic antimicrobial activity, it is able to tightly bind and inhibit many beta-lactamases (Aoki and Okuhara, 1980).

Members of the third generation of penicillins have activity against *P. aeruginosa.* This group includes ticarcillin and carbenicillin, both of which have reduced activity against gram-positive organisms and most enteric gram-negative rods. These compounds have activity

against *P. aeruginosa* as opposed to earlier generations of penicillins. They have activity against *Bacteroides fragilis* comparable to that of penicillin G. These compounds must be given in large doses, resulting in a significant sodium load, and they are susceptible to breakdown by beta-lactamases. However, the combination of ticarcillin and clavulanic acid is available.

The fourth generation of penicillins include the so-called ureidopenicillins - mezlocillin, azlocillin, and piperacillin. These compounds have a broad spectrum of activity that includes the spectrum for penicillin G plus activity for *H. influenzae,* enterococcus, *Klebsiella,* and *P. aeruginosa.* However, these agents are susceptible to hydrolysis by beta-lactamases. The broad spectrum of activity of the fourth generation penicillins has encouraged some clinicians to use them in combination with aminoglycosides for serious infections suspected of being caused by *P. aeruginosa.* The exact place of the fourth generation penicillins in antimicrobial therapy has not yet been clarified (Neu and Wise, 1982).

Pharmacokinetics

Methicillin is readily destroyed by the gastric acid and, therefore, is not used orally. Isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin) are acid stable and are absorbed from the gastrointestinal tract. Food delays absorption, so that peak serum concentrations are obtained later and are about one-half of those achieved in fasting patients. Oral cloxacillin produces serum level one and a half- to 2-fold higher than oxacillin, whereas, after oral dosing, dicloxacillin serum levels exceed those of cloxacillin by a factor of 1.5 to 2. The oral absorption of nafcillin is irregular. Penicillinase-resistant penicillins are widely distributed in various body fluids, but traverse the normal meninges poorly. Nafcillin achieves higher concentrations in the cerebrospinal fluid (CSF), both in patients with normal meninges and those with meningitis. Nafcillin is excreted by the liver and achieves extremely high biliary concentrations. It is excreted by the kidneys only to a small extent. Renal failure only slightly alters nafcillin pharmacokinetics, thus no dosage adjustment is required in patients with renal failure.

Cephalosporins

Cephalosporins inhibit bacterial cell wall synthesis and are thus classified as bactericidal antibiotics like penicillin. These antibiotics can be used as alternatives to penicillin in the treatment of pneumococcal and streptococcal infections when patients have a history of skin reaction to penicillin. Established indications include prophylaxis against wound infection in surgery. It is convenient to use a cephalosporin for initial therapy when the bacterial pathogen is unknown or is in the process of being identified, since these compounds possess a broad spectrum of antimicrobial activity. Cephalothin is active against many gram-positive bacteria including *S. aureus, S. pneumoniae,* and nonenterococcal streptococci. It is also active against some gram-negative rods, including *E. coli, K. pneumoniae* and *Proteus* (Rybak, 1982). Like the penicillins, the cephalosporins have been characterized into generations of compounds based on stepwise modifications of the parent compound cephalothin.

First-generation cephalosporins are active against most gram-positive cocci and gram-negative bacilli as discussed above. They are not effective against *Serratia, Enterobacter,* and

Enterococcus species; *P. aeruginosa; B. fragilis;* or *H. influenzae.*

Second-generation cephalosporins represented the next breakthrough in expanding the activity of cephalosporins because of their activity against *B. fragilis* (cefoxitin) and *H. influenzae* (cefaclor, cefamandole, cefonicid, ceforanide, and cefuroxime). Cefaclor is the only cephalosporin given orally that is effective against *H. influenzae* including ampicillin-resistant strains. It has been used to treat otitis media because of its activity against *H. influenzae, Diplococcus pneumoniae,* and *Streptococcus,* especially if ampicillin resistance is suspected. Cefuroxime has good CSF penetration. Both cefuroxime and cefoxitin are active against penicillinase-producing *N. gonorrheae* but must be administered parenterally.

Third-generation cephalosporins include compounds with activity against gram-negative bacteria. These agents are very active against *H. influenzae* and *N. gonorrheae* strains, which are highly resistant to the penicillins. These agents are active against *P. aeruginosa* and against anaerobes including *B. fragilis.* The so-called "extended spectrum" cephalosporins have gained gram-negative activity but have lost some activity against gram-positive organisms.

Cefotaxime has greater activity in vitro against many cephalosporin-resistant gram-negative organisms. Moxalactam is the most active third-generation cephalosporin against *B. fragilis,* with its activity in vitro approaching that of cefoxitin. In addition, moxalactam is active against *H. influenzae* and *N. gonorrheae.* Moxalactam, however, has been associated with severe bleeding disorders. Although cefoperazone has enhanced antipseudomonal activity, it cannot be relied on for single agent therapy for these infections. Compared with cefotaxime, ceftizoxime, and moxalactam, cefoperazone has less activity against most *Enterobacteriaceae.* Ceftriaxone has excellent CSF penetration. All third-generation cephalosporins require parenteral injection.

Moxalactam prolongs the prothrombin time, and patients have had bleeding complications that are related to moxalactam administration. Some bleeding complications have been reported with cefoperazone therapy as well. Patients with ethyl alcohol in their blood or tissue suffer acute symptoms of nausea, vomiting, flushing, and hypotension (disulfiram effect) when they receive moxalactam, cefoperazone, or cefmenoxime because of structural similarities (Eng, 1984).

Because none of the preceding beta-lactam antibiotics can be used alone to treat systemic *P. aeruginosa* infections, cefsulodin and ceftazimide were developed. Both of these agents have good activity against *P. aeruginosa.* The pharmacokinetics of cephalosporins is shown.

Adverse Reactions

Immediate reactions include anaphylaxis, bronchospasm, and urticaria. Delayed reactions include maculopapular rash, drug fever, and eosinophilia.

Although the chemical structures of penicillins and cephalosporins are similar, cross-sensitivity between these two groups is low. A patient with a history of allergic reaction of the delayed type to penicillin, such as a rash, probably has less than 5 per cent chance of

having the same reaction to a cephalosporin. However, in those patients with a history of anaphylactic or immediate reaction to penicillin, it is not recommended to administer a cephalosporin or any other beta-lactam drug. Large doses of cephalosporins have been associated with a positive Coombs test, which is rarely associated with hemolysis.

Imipenem

Imipenem is an antibiotic member of the new carbapenem class of antibiotics. The parent compound, thienamycin, is produced by *Streptomyces cattleya.* The carbapenems have the 4:5 fused ring lactam of the penicillins with a substitution of carbon for sulfur in an unsaturated 5-membered ring (Birnbaum et al, 1985). Thienamycin itself is unstable but the N-formidoyl derivative, imipenem, is stable.

It was soon discovered that carbapenem antibiotics undergo extensive metabolic inactivation in the kidney by a brush border enzyme, dehydropeptidase-1. A highly selective enzyme inhibitor was searched for and discovered. MK 0791, or cilastatin, significantly inhibits the degradation of imipenem (Birnbaum et al, 1985). This novel combination of a beta-lactam antibiotic (imipenem) and an enzyme inhibitor (cilastatin) has proved highly effective in experimental and clinical infections.

Imipenem has the broadest spectrum of the beta-lactam antibiotics (Birnbaum et al, 1985). It is active against gram-positive and gram-negative aerobic and anaerobic bacteria, including *Enterococcus, P. aeruginosa, Serratia* and all species of *Bacteroides* (Birnbaum et al, 1985). It is bactericidal even against bacteria resistant to aminoglycosides and the newer cephalosporins. Even beta-lactamase-producing *H. influenzae, Acinetobacter, Neisseria gonorrhoeae,* and *N. meningitidis* are susceptible to imipenem. However, activity is low or absent against *P. maltophila, P. cepacia, Streptococcus faecium, Flavobacteria,* and some diphtheroids. Also, a broad range of susceptibilities is found among methicillin-resistant staphylococci (Jones, 1985). This overall excellent antibacterial activity of imipenem is the result of the lack of a permeability barrier for bacterial penetration; a high affinity for penicillin-binding protein 2, a critical protein in cell wall synthesis of gram-negative bacteria, and for critical penicillin-binding proteins in gram-positive organisms; and above all, its great beta-lactamase stability (Neu, 1985a).

Neither imipenem nor cilastatin is appreciably absorbed orally and, therefore, must be given parenterally. Plasma half-life averages just less than 1 hour for both drugs with plasma clearance of about 200 mL/min (Drusano and Standiford, 1985). The half-life of imipenem is prolonged by renal failure, and the drug is removed by hemodialysis (Gibson et al, 1985). Adverse reactions among 2516 patients treated with this antibiotic include nausea, vomiting, local injection site reactions, and rash. A very low frequency of drug-relates seizures and transient elevation of the liver function test values were observed (Calandra et al, 1985). Clinical experience with imipenem/cilastatin has been fairly extensive. This drug combination was found to be efficacious in bacteremia (Eron, 1985), pneumonia (Salata et al, 1985), osteomyelitis (MacGregor and Gentry, 1985), urinary tract infections (Cox and Corrado, 1985), skin infections (Fass et al, 1985), surgical infections (Solomkin et al, 1985), and endocarditis (Donabedian and Freimer, 1985). Overall, imipenem and cilastatin appear to be relatively safe and highly effective. With regard to head and neck infections, the striking efficacy against anaerobes, including anaerobic bacteria, is notable. It should also be an

important agent for selected nosocomial infections (Neu, 1985b).

Aztreonam

Aztreonam is the first drug in a new category of the beta-lactam group of antibiotics. Its structure is composed of a single heterocyclic ring rather than the bicyclic rings of penicillins and cephalosporins. A series of synthetic monobactams were prepared and tested for biologic properties, and aztreonam was the first compound that was found to be useful in this series, the monobactams (Sykes and Bonner, 1985).

Aztreonam's antibacterial spectrum is unique among beta-lactam antibiotics. Unlike the majority of beta-lactam antibiotics, aztreonam exhibits little or no activity against gram-positive organisms, such as streptococci or staphylococci, or anaerobes. Aztreonam is primarily active against aerobic gram-negative bacteria commonly encountered in nosocomial infections. In vitro, aztreonam was found to be as active as, or more active than, cefotaxime, moxalactam, or gentamicin against the *Enterobacteriaceae.* Among non-*Enterobacteriaceae,* aztreonam was highly active against *H. influenzae* (including ampicillin-resistant strains), intermediately active against *Pseudomonas,* and poorly active against *Acinetobacter* (Sykes and Bonner, 1985).

The mechanism of action of aztreonam is through interference with bacterial wall synthesis. It has a high affinity for penicillin-binding protein 3, a protein important for cell division in aerobic gram-negative bacteria. Aztreonam is highly resistant to enzymatic hydrolysis by beta-lactamases produced by gram-positive and gram-negative bacteria.

Serum and urine levels of aztreonam after 0.5-, 1-, and 2-gram doses are potentially therapeutic for susceptible gram-negative organisms. The drug is widely distributed in body fluids and tissues. It is excreted primarily in the urine in an unchanged form. Protein binding is about 50 per cent and it is distributed to the extracellular water space. Serum half-life is 1.7 hours, confirming a dosing interval of 6 to 8 hours (Swabb, 1985). Aztreonam has proved to be extremely useful as sole therapy or in combination with other agents in treating urinary infections, pneumonia, skin infections, and selected intra-abdominal infections. It offers an alternative to using aminoglycosides and some of the broad-spectrum agents currently used (Neu, 1985c). There appears to be little cross-sensitivity between aztreonam and other beta-lactam antibiotics. None of 41 patients with documented IgE-reactive skin tests to various penicillin determinants demonstrated reproducible reactivity to any aztreonam fractions (Saxon et al, 1985). Side effects that have been reported to date include mild transient taste sensation during intravenous infusion, which was reported in 6 per cent of subjects. Mild fatigue, mild pruritus, erythematous rash, sneezing, and nasal congestion were reported in less than 3 per cent of subjects. Loose stools, fever, elevation of liver enzymes, and eosinophilia were found in a small percentage of subjects. No evidence of renal dysfunction was associated with aztreonam (Swabb, 1985). No apparent abnormalities of hemostasis were detected. An animal study failed to show any evidence of ototoxicity (Myhre et al, 1985). Detailed reports of aztreonam investigations have been reported in a recent symposium (Neu, 1985c). Dosages of beta-lactam antibiotics are given.

Vancomycin

Vancomycin is a glycopeptide antibiotic that was isolated from *S. orientalis.* Its major activity is against gram-positive bacteria with minimum inhibitory concentrations (MIC values) as low as 0.25 microg/mL for the most sensitive bacteria such as streptococci. At lower concentrations, vancomycin is bacteriostatic but becomes bactericidal at higher concentrations against streptococci, staphylococci, corynebacteria, and clostridia, with doses achieved clinically. However, only bacteriostatic concentrations can be achieved against enterococci. Gram-negative bacteria (other than some *Neisseria* strains), mycobacteria, and fungi are resistant to vancomycin (Perkins, 1982). Although in wide-spread use in the late 1950s and early 1960s, considerable problems with side effects of chills, fever, and occasional hypotension were encountered (Cunha and Ristuccia, 1984). At least some of the side effects were caused by impurities in the preparations, which have subsequently undergone better purification (Riley, 1970). Currently, vancomycin has very few side effects, and is considered one of the safest antibiotics available (Cunha and Ristuccia, 1984). In the late 1970s, clinicians began to recognize the value of vancomycin in the treatment of severe gram-positive infections such as bacterial endocarditis, especially in patients with known allergy to penicillin. Vancomycin has also been used to treat gram-positive infections in dialysis patients (Esposito and Gleckman, 1977; Polk et al, 1981). The emergence of methicillin-resistant *S. aureus* and *S. epidermidis* strains particularly has brought about a renaissance in the use of vancomycin (Watanakunakorn, 1982). Vancomycin is also useful in the treatment of staphylococcal enterocolitis and pseudomembranous colitis caused by toxogenic *Clostridium difficile,* since this antibiotic is not appreciably absorbed from the gastrointestinal tract (Perkins, 1982).

The mechanism of antibiotic action is thought to be an interference with cell wall peptidoglycan synthesis (Perkins, 1982).

The peak blood levels of vancomycin after a 1-gram intravenous injection are 25 to 40 microg/mL. The serum half-life is 6 hours. The usual adult dose is 500 mg every six hours, or 1 gram every 12 hours intravenously. Usual dosages for children are 25 to 40 mg/kg per day. Dosage adjustments are needed in patients with renal insufficiency and in the elderly (Cutler et al, 1984). In premature infants under 1 kg, a loading dose of 25 mg/kg is recommended, followed by maintenance doses of 15 mg/kg every 12 hours; infants weighing more than 1 kg should receive a loading dose of 1.5 mg/kg and a maintenance dose of 10 mg/kg every 12 hours. Serum vancomycin therapy should be monitored to optimize therapy (Gross et al, 1985).

Toxicity includes ototoxicity, anaphylaxis, nephrotoxicity, local thrombophlebitis, drug fever, and transient neutropenia in adults but not in children or infants. Children have been reported to develop skin rashes consistent with the "red neck" syndrome (Gross et al, 1985). Although therapeutically synergistic with aminoglycosides in the treatment of serious infections caused by enterococci or *S. viridans,* the toxicity may also be enhanced by such combination therapy. It has been recommended that serum levels of vancomycin do not exceed 50 microg/mL (Watanakunakorn, 1982).

Vancomycin has been suggested as the drug of first choice for treating infections caused by nondiphtheric *Corynebacteria* in an immunocompromised host (Pearson et al,

1977). Vancomycin is also recommended for the treatment of serious staphylococcal infections of the central nervous system, especially in patients with implanted foreign materials, such as ventriculoperitoneal shunts (Banner and Ray, 1984).

Aminoglycosides and Aminocyclitols

Aminoglycoside antibiotics are a class of antibacterial compounds whose central amino sugar is 2-deozystreptamine, a diamino hexose. Additional specific amino sugars are connected to 2-deozystreptamine by single glycosidic linkages (Jackson, 1977). Streptomycin, which has streptose, a monoamino hexose instead of the 2-deoxystreptamine, is often included among the group of aminoglycoside antibiotics because of similarities in the rest of its structure and in its biologic properties. Other antibiotics, such as spectinomycin, contain aminosugars, but the other structural portions and properties are quite different. These drugs are more correctly referred to as aminocyclitol antibiotics. The aminoglycosides include three families: the kanamycins, the gentamicins, and the neomycins.

The aminoglycosides are bactericidal. They penetrate the bacterial cell wall and cytoplasmic membrane and act on the ribosome by binding to proteins in the 30 s segment. Protein synthesis is thereby inhibited, and cell death ensues (Edson and Keys, 1983). In order to reach the site of action, the drug must be transported across the cell membrane. This involve primarily active transport.

All of the 2-deoxystreptamine aminoglycosides have similar pharmacologic properties. However, larger doses of kanamycin and amikacin are required to produce therapeutic concentrations. The drugs are rapidly absorbed after intramuscular injection, but there is minimal absorption in the intestine. Peak concentrations are reached in the serum 30 to 90 minutes after intramuscular injection. The half-life in patients with normal renal function is about 2 hours. Protein binding is very low, between 0 to 20 per cent. Eighty-five to ninety-five per cent of the drug is excreted by glomerular filtration into the urine within 24 hours. Transport into cerebrospinal fluid is small, with drug concentrations reaching 8 to 25 per cent of plasma concentration. Sputum levels achieved are about 10 per cent of plasma levels.

The pharmacokinetics of the aminoglycosides are consistent with a two-compartment model. Small differences in renal functions can cause striking effects on the half-life of aminoglycosides. The dosage and administration are given. Some specific discussions of the individual indications of specific compounds in this category follow.

Streptomycin

Streptomycin in combination with penicillin G, ampicillin or vancomycin is used for enterococcal endocarditis. Streptomycin is also used to treat tularemia, plague, and is combined with tetracycline to treat brucellosis. Streptomycin is used in combination with agents such as isoniazid, ethambutol, and rifampin to treat tuberculosis. Streptomycin crosses the placenta and may cause fetal ototoxicity.

Kanamycin

This drug is used as a second choice agent for tuberculosis and is a nonabsorbable oral agent for preoperative bowel surgery and for hepatic coma.

Amikacin

Amikacin is a semisynthetic derivative of kanamycin. Amikacin is more effective against gram-negative bacilli than kanamycin and is also effective against *P. aeruginosa.* Amikacin is effective against some strains of gentamicin-resistant organisms and may be the aminoglycoside of choice for treating these organisms.

Gentamicin

This antibiotic is useful to treat serious infections caused by *P. aeruginosa, Enterobacteriaceae,* various other sensitive gram-negative organisms, and *S. aureus,* including some methicillin-resistant strains. Gentamicin is rapidly absorbed after intramuscular injection and peak serum levels of 3.5 to 5.0 microg/mL occur in about 1 hour. Serum peak levels should not exceed 8 to 10 microg/mL, and trough levels should not exceed 2 microg/mL to avoid toxicity. Intrathecal administration may be required in cases of severe gram-negative meningitis (Rahal, 1974).

Tobramycin

The indications for tobramycin are similar to those for gentamicin. Tobramycin is more active in vitro than gentamicin against *P. aeruginosa.* Activity equal to gentamicin has been demonstrated against *E. coli, Klebsiella, Enterobacter,* and *Proteus.* Synergism with ureidopenicillins (carbenicillin, ticarcillin, and piperacillin) has been shown against some strains of *P. aeruginosa,* including those causing malignant external otitis, and with penicillin against enterococci.

Netilmicin

Netilmicin is used for gentamicin-resistant strains of *Pseudomonas.* In gentamicin-sensitive strains, it may be somewhat less effective than gentamicin. Netilmicin appears to be considerably less ototoxic than other aminoglycosides (Kahlmeter and Dahlager, 1984).

Neomycin

Neomycin is rarely used systematically because of a severe ototoxicity and nephrotoxicity. Its current use is limited to topical application, oral administration for hepatic coma, and presurgical bowel preparation (Edson and Keys, 1983).

Adverse Reactions

A variety of hypersensitivity reactions can occur following the administration of streptomycin. These include skin rashes, eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, and anaphylactic shock (Sande and Mandell, 1985). Local reactions

may occur at the site of intramuscular injection.

Nearly 75 per cent of patients given 2 grams of streptomycin daily for 60 to 120 days may exhibit vestibular disturbances. An acute stage, preceded by headache of 1 or 2 days duration, becomes manifest as nausea, vomiting, and dysequilibrium for 1 to 2 weeks. Vertigo in the upright position and difficulty sitting or standing without visual cues are prominent findings. The acute stage is suddenly replaced by chronic labyrinthitis, characterized by ataxia. This chronic stage is eventually replaced by a compensatory stage, in which adaptation is accomplished by vision and proprioception. Full recovery may require 12 to 18 months and some patients never recover. Tinnitus and sensorineural hearing loss may also occur. Optic nerve dysfunction may become manifest as an enlarging blind spot. Peripheral neuritis and neuromuscular blockade may occur. Nephrotoxicity is the most frequent serious complication (Sande and Mandell, 1985).

A review of prospective studies of nephrotoxicity and ototoxicity was reported by Kahlmeter and Dahlager (1984). Gentamicin and tobramycin were the most nephrotoxic, but amikacin and gentamicin were the most cochleotoxic. Netilmicin was the least toxic to the kidneys and the cochlea as well as the vestibular system. Compared with penicillins and cephalosporins, the margin between toxic and therapeutic doses is narrow for the aminoglycosides (Edson and Keys, 1983). Therefore, knowledge of serum antibiotic levels is essential to achieve the desired therapeutic effect and to minimize toxicity. For determination of peak serum levels, blood should be drawn 1 hour after the first maintenance dose and, for determination of the through level, just preceding the next dose. Various nomograms have been devised to plan dosage and intervals in patients with renal failure. Rising through levels may be an early indicator of nephrotoxicity. Detailed recommendations for monitoring ototoxicity of aminoglycosides have been published elsewhere (Rybak and Matz, 1988).

Metronidazole

Metronidazole is a nitroimidazole compound which was found to have trichomonacidal activity. In addition to this action, metronidazole is amebicidal and has been found to kill *Giardia lamblia* and has activity against the guinea worm in dracontiasis. An important finding was that metronidazole is bactericidal against anaerobes, including *B. fragilis.* It may be valuable in treatment of deep neck abscesses, chronic sinusitis, and infected cholesteatomas (Fairbanks, 1985). Metronidazole is administered either by the oral or the intravenous route and rarely appears to cause toxicity. Metronidazole readily penetrates the blood-brian barrier and may cause CNS side effects. It readily relieves the pain of Vincent's angina and can also be used to treat pseudomembranous enterocolitis. The dose for anaerobic infections includes a loading dose of 15 mg/kg intravenously, followed in 6 hours by a maintenance dose of 7.5 mg/kg every 6 hours.

Rifampin

Rifampin is an antibiotic with activity against pulmonary tuberculosis. It is also useful as a prophylactic agent in nasopharyngeal carriers of *N. meningitidis* and *H. influenzae* and can be given to infants and children in close contact with patients having documented *H. influenzae* systemic infections, such as meningitis or epiglottitis. Rifampin can be used in combination with aminoglycosides or cephalosporins to treat severe staphylococcal infections.

The dose for tuberculosis is 600 mg once daily in adults, given 1 to 2 hours after a meal. Children are given 10 mg/kg but not more than 600 mg daily. For prophylaxis of meningococcal disease, adults are given 600 mg twice daily and children 20 mg/kg daily for 2 days (Sande and Mandell, 1985).

Erythromycin

Most gram-positive cocci, aerobic and anaerobic, are susceptible to erythromycin; however, resistant strains are being reported. Increased interest in erythromycin has occurred because of its activity against *Legionella pneumophila.* Most gram-negative bacteria are resistant.

Erythromycin is an organic base classified as a macrolide antibiotic. It acts on the 50 s ribosome to inhibit RNA-dependent protein synthesis. Erythromycin is mainly bacteriostatic. Peak blood levels after 500 milligram oral doses are 1.0 to 2.5 microg/mL at 30 to 90 minutes after administration. The serum half-life is 1.5 to 2.5 hours. The usual oral dosage is 250 to 500 mg every 6 hours; intravenously, 1 gram every 6 hours is the recommended dosage. Erythromycin base is destroyed by gastric acid and is used primarily as a bowel preparative antibiotic for colon surgery. Various esters are available that are better absorbed than the stearate salt after oral administration. Excretion occurs primarily by the gastrointestinal tract, so that no dosage adjustment is required in renal failure. This drug is particularly useful in the treatment of infections caused by *S. aureus* when beta-lactam antibiotics cannot be used because of allergy or bacterial resistance.

Adverse reactions are often gastrointestinal, with nausea, epigastric discomfort, and diarrhea. Cholestatic jaundice and hepatitis occur rarely but are serious side effects that occur exclusively with the estolate salt. Intravenous administration may cause thrombophlebitis. At least 32 cases of bilateral, sensorineural hearing loss, which is typically uniform across frequencies, have been reported in association with high doses of intravenously or orally administered erythromycin (Rybak and Matz, 1988).

Lincomycin and Clindamycin

Lincomycin is an antibiotic produces by *S. lincolnesis,* and clindamycin is a derivative. These drugs resemble macrolides, in their chemistry and antibacterial spectrum. These drugs are active against gram-positive bacteria and most anaerobes including *B. fragilis.* Gram-negative bacteria are generally resistant. These drugs are usually considered bacteriostatic antibiotics that inhibit the initiation of peptide chain synthesis. Peak blood levels of clindamycin after 300 milligrams orally are 3 to 5 microg/mL 35 to 75 minutes after administration. Serum half-life is 2 to 3 hours but may be prolonged by liver disease. The usual oral adult dose is 150 to 450 milligrams every 6-8 hours and pediatric doses are 8 to 20 mg/kg per day. No dosage modifications are needed for renal failure. Parenteral doses are 300 to 600 mg every 6 to 8 hours intramuscularly or intravenously (Wilson and Cockerill, 1983).

The most serious complication is pseudomembranous colitis, which occurs in about 0.01 per cent of cases and is caused by *Clostridium difficile* exotoxin. Uncomplicated diarrhea occurs more frequently. Transient abnormalities of liver function and hypersensitivity

reactions such as rash or urticaria can occur. Shock and cardiac arrest with rapid intravenous administrations have been reported.

Tetracyclines

Tetracyclines are active against many gram-positive and gram-negative bacteria (except *P. aeruginosa* and *Serratia*), *Rickettsia,* and *Mycoplasma.* Minocycline and doxycycline are more active against opportunistic pathogens such as *P. cepacia, P. maltophila,* and *Acinetobacter.* Tetracyclines are bacteriostatic and act by inhibiting protein synthesis in bacteria. Peak blood levels after oral administration of 250 mg are 1 to 3 microg/mL at 1 to 2 hours after administration. Serum half-life is 7 hours for chlortetracycline, 15 hours for doxycyline, and 17 hours for minocycline. Excretion is primarily through the gastrointestinal tract and kidneys. The usual adult dosage for minocycline is 200 mg initially, followed by 100 mg every 12 hours. The pediatric oral dose is 2 to 4 mg/kg per day, but tetracycline should be avoided in children under 8 years of age. Gastrointestinal side effects such as nausea, vomiting, anorexia, and diarrhea are common. Hepatotoxicity and nephrotoxicity can occur. Outdated tetracyclines may cause a Fanconi-like syndrome. Tetracyclines cause a discoloration of teeth in children and could disrupt bone growth in the fetus and infants. Photosensitivity, thrombophlebitis with intravenous administration, and vestibular toxicity (minocycline) have been reported. Inhibition of gastrointestinal absorption of tetracyclines is thought to occur by chelation by substances such as milk (Goth, 1981). For that reason, tetracycline should not be given with milk or antacids, which contain aluminum, magnesium, or calcium.

Chloramphenicol

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of activity similar to tetracycline. It is useful in the treatment of various rickettsial and enteric bacterial infections (including typhoid fever). It is active against streptococci and staphylococci; anaerobes, including *B. fragilis;* and *H. influenzae,* including ampicillin-resistant strains. Peak blood levels after oral dosage of 500 mg are 3 to 6 microg/mL at 2 hours. Serum half-life is 2 to 3 hours. Chloramphenicol is one of the most effective antibiotics in penetrating the blood-brain barrier, reaching over 50 per cent of serum concentrations in CSF when the meninges are not inflamed. The drug is well distributed throughout the body tissues. It can be given orally or intravenously but is not effective by the intramuscular route. The adult oral dose is 250 to 500 mg every 6 to 8 hours or 1 gram every 6 to 12 hours intravenously. The pediatric dose is 25 to 50 mg/kg daily. In neonates, 15 to 25 mg/kg per day is recommended.

Dose-related bone marrow toxicity such as anemia, low reticulocyte count, and leukopenia are usually reversible. Aplastic anemia is the most serious complication reported. It is irreversible, not dose-related, and occurs in one per 25.000 to 50.000 cases. Gastrointestinal side effects, such as nausea, vomiting, diarrhea, and pseudomembranous colitis, can occur. Chloramphenicol attaches to the bacterial ribosomes (50 s subunits) and prevents the binding of amino acids, thus interfering with the growth of the peptide chain in bacteria. The action of this antibiotic seems to be largely bacteriostatic. In neonates or premature infants, a potentially fatal toxic side effect known as the gray syndrome can occur, which is related to the immaturity of the glucuronyl transferase enzyme of the liver of the neonate, which normally detoxifies chloramphenicol. Symptoms of the gray syndrome include

cyanosis, vascular collapse, and elevated chloramphenicol levels in the blood. Chloramphenicol is available for topical use as an otic and ophthalmic preparation. Ototoxicity has been reported when high doses of chloramphenicol were used in some patients (Rybak and Matx, 1988).

Fosfomycin

Fosfomycin is a unique epoxide antibiotic that contains phosphate within its structure. This antibiotic is bactericidal and acts by interfering with cell wall synthesis. Fosfomycin has been on the market in Japan since 1980 but is not yet commercially available in the United States. It is active against *S. aureus* and gram-negative bacteria, such as *E. coli, Serratia, Proteus,* and *P. aeruginosa. S. pneumoniae* and *S. haemolyticus* are occasionally sensitive, but anaerobes are typically resistant. Peak blood levels of 3.5 microg/mL are found 1 hour after an oral dose of 500 mg. The serum half-life is 2 hours. In orthopedic infections, this drug can be used as an agent of first choice if beta-lactams cannot be used. It is thought to penetrate sclerotic foci of osteomyelitis better than other drugs because of its low molecular weight (Hayashi, 1984). Fosfomycin can be combined with a beta-lactam or with an aminoglycoside because of synergistic effects, and perhaps the combination could prevent the emergence of fosfomycin-resistance (Hayashi, 1984). Not only is fosfomycin synergistic with aminoglycosides against infections, but also animal experiments suggest that fosfomycin protects the patient against the nephrotoxicity and ototoxicity caused by aminoglycosides (Ohtsuki et al, 1983). The adult oral dose is 0.5 to 1.0 gm every 6 to 8 hours, and the same dose is given intravenously every 6 to 12 hours. The pediatric oral dose is 40 to 120 mg/kg per day, and the intravenous dose is 50 to 100 mg/kg every 12 hours (Hayashi, 1984).

Polymyxins

The polymyxins are cationic detergents with molecular weights of around of 1000 daltons. Polymyxin B and E (colistin) are the most commonly used members of this group. These drugs are bactericidal by virtue of their detergent action, which disrupts the cell wall membrane complex. Peak blood levels after a 100-mg intramuscular injection of colistin are 4 to 8 microg/mL 30 minutes after administration. The serum half-life is 1.5 to 3 hours for colistin and 4 to 7 hours for polymyxin. Excretion is via the kidneys. Systemic administration of polymyxins is rarely employed except in serious life threatening infections caused by *P. aeruginosa.* Polymyxins can be applied topically as a suspension or solution (eg, otic drops). They have also been used for closed irrigation for the treatment of osteomyelitis (Hayashi, 1984). Nephrotoxicity has been reported in about 20 per cent of the patients receiving colistin injections. Symptoms of neurotoxicity include paresthesias, dizziness, ataxia and weakness. Respiratory arrest caused by neuromuscular blockade is reportedly rare. Oral administration can be used for alimentary tract disinfection, since these drugs are not absorbed.