FLUOROQUINOLONES

Nalidixic acid is one of the older members of the quinolone class of synthetic antimicrobial agents that have been used for the treatment of lower urinary tract infections. Drugs of this class are of relatively minor significance because of their limited therapeutic ability and the rapid development of bacterial resistance.

The important quinolones are synthetic fluorinated analogs of nalidixic acid, these fluorinated derivatives such as ciprofloxacin, levofloxacin, and others have greatly improved antibacterial activity compared with nalidixic acid and achieve bactericidal levels in blood and tissues. They are orally effective for the treatment of a wide variety of infectious diseases, have relatively few side effects and microbial resistance does not develop rapidly.

Mechanism of action:

Fluoroquinolones are broad spectrum bactericidal drugs. Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Inhibition of DNA gyrase prevents the relaxation of supercoiled DNA that is required for normal transcription and replication. Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division. For many gram positive bacteria such as **S. aureus**, topoisomerase IV is the primary target. For many gram-negative bacteria such as ***E.coli***, DNA gyrase is the primary quinolone target.

Antibacterial activity:

The antibacterial spectrum of fluoroquinolones and the drugs involved comprise three main groups or generations:

(1)Activity against gram-negative organisms, including ***Pseudomonas***, and some gram positive organisms including ***S. aureus***. The drugs involved are **ciprofloxacin, norfloxacin and ofloxacin**. Ciprofloxacin is the most potent fluoroquinolone against ***Pseudomonas***.

(2)Activity the same as first group, plus expanded gram-positive coverage including ***S. pneumoniae***. Drugs of this category include **levofloxacin and gatifloxacin.**

(3)Activity the same as second group, plus activity against **anaerobes**. This includes **trovafloxacin**.

In addition, fluoroquinolones are also active against agents of atypical pneumonia such as *Mycoplasma and Chlamydia* and against intracellular pathogens such as *Legionella* species and some *Mycobacteria* including *Mycobacterium tuberculosis*.

Mechanism of bacterial resistance:

Three mechanisms of resistance are known:

1-Some types of efflux pumps can act to decrease intracellular quinolone concentration.

2-In gram negative bacteria, plasmid mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones.

3-Mutations in DNA gyrase or topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drugs' effectiveness.

Pharmacokinetics:

Fluoroquinolones are rapidly and almost completely absorbed from GIT (bioavailability of 80–95%). Absorption is impaired when they are given with food, antacids or milk; therefore, oral fluoroquinolones should be taken 2 hours before or 4 hours after these products. Peak serum concentrations obtained after oral administration are very near to those achieved with I.V. administration.

Fluoroquinolones have a large volume of distribution; their concentration in tissues often exceeds serum drug concentrations.

Trovafloxacin penetrates well non inflamed meninges. The serum half-lives range from 3-5 hours for drugs of the first group, **7** hours for the second group and 11 hours for the third group. The long half-life of the newer fluoroquinolones allows once or twice daily dosing.

Most quinolones are cleared predominantly by the kidney (Ofloxacin and levofloxacin are exclusively eliminated by the kidney), and dose must be adjusted for renal failure. Pefloxacin and moxifloxacin are metabolized predominantly by the liver and should not be used in patients with hepatic failure, trovafloxacin is eliminated primarily non renally (hepatic or GIT).

Adverse effects:

Fluoroquinolones are extremely well tolerated.

l-GIT manifestations are the most common adverse effects and include nausea, vomiting, abdominal pain and diarrhea.

2-Headache and dizziness have occasionally been observed. Rarely, hallucinations, delirium, and seizures have occurred, predominantly in patients who also were receiving theophylline or a nonsteroidal anti- inflammatory drug.

3-Rashes including photosensitivity reactions can occur.

4-Acute renal failure and anaphylaxis rarely occur.

5-Rare but serious hepatic damage including liver failure resulting in death was observed in patients receiving trovafloxacin. For this reason the use of trovafloxacin has been restricted to serious or life threatening infections where the benefits of therapy outweigh the risks.

The prescribing information for gatifloxacin includes a contraindication in diabetic patients due to serious reports of hypoglycemia and hyperglycemia. Risk factors for this adverse effect include older age, renal insufficiency, and concomitant therapy with glucose-altering medications.

Fluoroquinolones may damage growing cartilage and cause bone and joint damage and that is why they are, generally, not used in patients under 18 years. They are also contraindicated during pregnancv and lactation.

Clinical uses:

l-Urinary tract infections, even when caused by multidrug resistant bacteria as *Pseudomonas*.

2-Prostatitis caused by sensitive bacteria.

3-Sexually transmitted diseases such as gonorrhea and chlamydial urethritis or cervicitis.

4-Bacterial diarrhea caused by *Shigella. Salmonella or toxigenic E. coli*.

5-Bone, joints and soft tissue infections.

6-Respiratory tract infections: Levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin, so-called respiratory fluoroquinolones, with their enhanced gram-positive activity and activity against atypical pneumonia agents (eg, chlamydia, mycoplasma, and legionella), are effective and used increasingly for treatment of upper and lower respiratory tract infections.

7-Ciprofloxacin is a drug of choice for prophylaxis and treatment of anthrax.

8-Prophylaxis against infections in neutropenic patients (impaired host defense mechanisms).

URINARY ANTISEPTICS

Urinary antiseptics are oral agents that exert antibacterial activity in the urine but have little or no systemic antibacterial effect because effective concentrations are not achieved in the plasma with safe doses. Their usefulness is limited to lower urinary tract infections as they are concentrated in the renal tubules. Prolonged suppression of bacteriuria by means of urinary antiseptics may be desirable in chronic urinary tract infections in which eradication of infection by short-term systemic therapy has not been possible.

METHENAMINE (Methenamine Mandelate & Methenamine Hippurate):

Methenamine mandelate is the salt of mandelic acid and methenamine and possesses properties of both of these urinary antiseptics. Methenamine hippurate is the salt of hippuric acid and methenamine.

At acidic pH below 5.5, methenamine decompose producing formaldehyde, which is antibacterial.

Methenamine + water → formaldehyde + ammonia

It is bactericidal for gram-positive and gram-negative microorganisms and is more effective in an acid urine.

Acidifying agents (eg, ascorbic acid) may be given to lower urinary pH below 5.5.

Antibacterial activity

Nearly all bacteria are sensitive to free formaldehyde and bacterial resistance to formaldehyde does not develop.

Urea splitting bacteria, such as *Proteus*, tend to raise pH of urine and inhibit the release of formaldehyde and thus are not affected by methenamine.

Pharmacology and toxicology

l-Methenamine is orally administered, distributed throughout the body fluids, but no decomposition occurs at pH 7.4 and thus systemic toxiciy does not occur. It is eliminated in urine.

2-Methenamine is primarily used for chronic suppressive therapy of lower urinary tract infections.

3-Untoward effects include GIT distress. At high doses; albuminuria, hematuria and rash may develop.

4-Because ammonia is produced on decomposition, it should not be given to patients with hepatic insufficiency. Methenamine mandelate is contraindicated in patients with renal insufficiency because mandelic acid may precipitate.

Sulfonamides must not be used concomitantly with methenamine because it reacts with formaldehyde forming insoluble compounds.

NITROFURANTOIN:

Antibacterial activity:

Nitrofurantoin is bacteriostatic and bactericidal for many gram-positive and gram-negative bacteria but *P aeruginosa* and many strains of proteus, klebsiella and enterobacter are resistant.

Sensitive bacteria reduce nitrofurantoin to toxic products that inhibits various enzymes and damages DNA. Activity is greater in acidic urine.

Pharmacology and toxicology:

l-Nitrofurantoin is rapidly and completely absorbed from the GIT.

Antibacterial concentrations are not achieved in plasma at recommended doses because the drug is eliminated rapidly. It colors the urine brown.

2-The most common side effects are:

i- Anorexia, nausea, vomiting and diarrhea.

ii-hypersensitivity reactions which include fever, chills, leukopenia and hepatotoxicity.

Uses:

-Current uses include the treatment of uncomplicated urinary tract infection (UTI_s) and prophylaxis against (UTI_s) in people prone to recurrent (UTI_s).

Increasing bacterial antibiotic resistance to other commonly used agents such as trimethoprim-sulfamethoxazole and fluoroquinolones; make nitrofurantoin an important alternative oral agent for treatment of uncomplicated urinary tract infection.

Macrolides

ERYTHROMYCIN, CLARITHROMYCIN, AZITHROMYCIN

This group of antibiotics is so named because they possess a macrocyclic lactone ring, the main agent is erythromycin. Newer agents include clarithromycin and azithromycin.

ERYTHROMYCIN

Mechanism of action

Erythromycin inhibits protein synthesis by binding reversibly to the 50 S ribosomal subunits of sensitive microorganisms. Protein synthesis is inhibited as aminoacyl translocation reactions are blocked. Its binding site to the 50 **S** ribosomal subunit appears to be the same as that of chloramphenicol and clindamycin and so the three agents could compete if given concurrently.

Antimicrobial spectrum

Erythromycin is bacteriostatic but can be bactericidal in high concentrations
against very susceptible organisms.

Erythromycin is effective against gram-positive bacteria but not against most gram-negative organisms, the exceptions being *Gonococci* and to a lesser extent *H. influenzae*. *Mycoplasma, Legionella* and some *Chlamydia* are sensitive.

Although some strains of staphylococci are sensitive, the dose for inhibitory action is great. In addition, resistance may develop during treatment.

Resistance

Resistance to macrolides results from at least three types of plasmid controlled alterations:

l-Decrease in permeability of the drug through the cell envelope as occurs with staph. epidermidis.

2-Esterases produced by *Enterbacteriacae* cause hydrolysis of erythromycin.

3-Reduced binding for erythromycin on the bacterial ribosome.

Pharmacokinetics

Erythromycin base is inactivated by gastric acids and must be administered with enteric coating. It is incompletely but adequately absorbed from the upper part of intestine, food interferes with absorption. Esters of erythromycin base as erythromycin estolate is less susceptible to acid than is the parent compound; it is better absorbed than other forms of the

drug and is not appreciably altered by food. However, only the base is microbiologically active.

The drug diffuses readily into most tissues including prostatic fluid and the placenta but does not cross the blood brain barrier.

Only 2-5 % of orally administered erythromycin is excreted in active form in urine. The drug is concentrated in the liver where some is inactivated but it is mainly excreted as the active form in the bile.

Untoward effects

l-Hypersensitivity reactions including skin rashes and fever may occur.

2-Cholestatic hepatitis with jaundice is a striking side effect and is produced mainly by erythromycin estolate (rarely with ethyl succinate or stearate). The illness starts after 10-20 days of treatment and the manifestations usually disappear within a few days after cessation of drug therapy.

3-Transient auditory impairment may occur after large doses given I.V. or orally.

4-Oral administration especially of large doses is very frequently accompanied by epigastric distress with abdominal cramps, nausea, vomiting, and diarrhea. Erythromycin has been shown to act as a ***motilin receptor agonist*** with resulting stimulation of GIT motility.

5-I.M. injections may cause pain and I.V. injection may be followed by local thrombophlebitis

Therapeutic Uses

1-Mycoplasma pneumoniae infections.

2-Legionella infections: erythromycin is currently recommended for the treatment of pneumonia encountered in Legionnaires' disease.

3-Chlamydia infections: tetracycline is just as effective and erythromycin is alternative to tetracycline in patients with uncomplicated urethral, endocervical, rectal or epididymal infections. It is the drug of choice for urogenital infections during pregnancy, and is preferred for chlamydial pneumonia of infancy.

4-Diphtheria: erythromycin is very effective for eradicating the carrier state. Neither erythromycin nor any other antibiotic alters the course of an acute infection with the diphtheria bacillus or the risk of complications. Antitoxin is indicated in treatment of acute infection.

5-Pertussis infection: administered early in the course of whooping cough erythromycin may shorten the duration of illness.

Macrolides are effective in streptococcal and pneumococcal disease in penicillin allergic patients, though resistance is increasing. Recent reports demonstrate a lack of benefit in the prevention of cardiac events.

AZITHROMYCIN, CLARITHROMYCIN

Azithromycin and clarithromycin are structural analogs of erythromycin that have similar mechanisms of action. They have several distinct advantages over erythromycin including longer half-life allowing once or twice daily administration, higher tissue concentrations and fewer GIT adverse effects. They also have enhanced antimicrobial activity.

Antimicrobial spectrum

Like erythromycin, these macrolide antibiotics are active against gram-positive bacteria, *Legionella, Mycoplasmas and Chlamydia*.

They have also a broader spectrum with enhanced activity against *Mycobacterium avium-intracellulare* (which can infect patients with AIDS and elderly patients with chronic lung disease).

Clarithromycin has good activity against Mycobacterium leprae.

Pharmacokinetics:

Both azithromycin and clarithromycin are well absorbed from GIT; they are more acid stable than erythromycin.

They are distributed to tissues and phagocytic cells. Azithromycin is unique in having extensive tissue distribution (Vd is 31 liters / kg).

In the liver azithromycin undergoes some hepatic metabolism to inactive metabolites but biliary excretion is the major route of elimination. Clarithromycin is eliminated by renal and nonrenal mechanisms; it is metabolized in the liver to several metabolites, the active l4-hydroxy metabolite is the most significant.

Unwanted effects

Both drugs are well tolerated and cause little nausea or diarrhea. Reversible dose related hearing loss can occur when high doses are used to treat M. avium infections.

Clinical uses

Azithromycin and clarithromycin are expensive alternatives to erythromycin.

1-They are recommended as first line therapy in the treatment of *M.* avium and other infections associated with AIDS (e.g. toxoplasmosis, cryptosporidiosis).

2-Azithromycin is an alternative to doxycycline in patients with uncomplicated urethral, endocervical, rectal or epididymal infections due to Chlamydia.

3-Clarithromycin in combination with omeprazole and amoxicillin, is effective for treatment of peptic ulcer related to H. pylori infection.

AMINOGLYCOSIDES

STREPTOMYCIN, GENTAMICIN, TOBRAMYCIN, AMIKACIN, NETILMICIN, KANAMYCIN, NEOMYCIN.

They are bactericidal drugs sharing chemical, antimicrobial, pharmacological and toxic characteristics. They are most active against aerobic gram-negative bacteria. Their action against anaerobes and most gram-positive bacteria is limited.

Mechanism of action:

They are rapidly bactericidal for susceptible organisms by producing irreversible inhibition of protein synthesis. Although most inhibitors of microbial protein synthesis are bacteriostatic, the aminoglycosides are bactericidal.

(1)The initial event in the mechanism is penetration through the cell envelope. This is, in part, an active transport process and, in part, passive diffusion. The latter can be greatly enhanced by cell wall active drugs as penicillins. Since the active transport is an oxygen dependent process, aminoglycosides are relatively ineffective against strict anaerobes.

(2)Once inside the cell they bind to 30 S ribosomal subunit.

(3)Ribosomal protein is inhibited through their ability to:

i- interfere with the "initiation complex" of peptide formation.

ii-induce misreading of the code on mRNA template. This causes incorporation of incorrect amino acids into the peptide with the formation of abnormal or malfunctional proteins which are fatal to the microorganism.

Microbial resistance:

Resistance may develop through the following mechanisms:

l-Alteration in the cell surface which interferes with the permeation or transport of aminoglycosides into the cell. This may be chromosomal (e.g. *Enterococci*) or plasmid-controlled (e.g. gram-negative bacteria).

2-The receptor protein on 30S ribosomal subunit may be deleted or altered as a result of chromosomal mutation.

3-Microorganisms secrete enzymes that inactivate aminoglycosides by adenylation, acetylation or phosphorylation.

4-Anaerobes are resistant to aminoglycosides because oxygen dependent transport is not functional in anaerobes.

Absorption. distribution and excretion:

Aminoglycosides are highly polar compounds that do not enter cells readily and are absorbed poorly from intact GIT but may be absorbed if ulcerations are present. They are absorbed well from IM. sites and peak plasma concentrations occur in 30-90 minutes.

Being highly polar compounds, aminoglycosides do not cross well into the CNS (even if the meninges are inflamed) and the eye.

Aminoglycosides have **concentration-dependent killing;** that is, increasing concentrations kill an increasing proportion of bacteria and at a more rapid rate. They also have a significant **postantibiotic effect,** in which residual bactericidal activity persists even after the serum concentration has fallen below the minimum inhibitory concentration. These properties account for the efficacy of once-daily dosing regimens.

There is no significant metabolic breakdown and they are eliminated mainly unchanged. Excretion is mainly by glomerular filtration and is greatly reduced with impaired renal function. In persons with impaired renal function there is danger of drug accumulation and increased incidence of ototoxicity and nephrotoxicity, as both are dose dependent.

Adverse effects:

l-Ototoxicity. All aminoglycosides are capable of affecting both cochlear (hearing) and vestibular or labyrinthine (equilibrium) divisions of the eighth cranial nerve. Cochlear toxicity is manifested by tinnitus and hearing loss while vestibular toxicity is manifested by nausea, vertigo and unsteady gait. Deafness and vestibular damage may not appear until several days after the drug is stopped and may progress to permanent and complete loss of hearing.

Regarding ototoxicity:

a-There is some preferential toxicity among aminoglycosides. Streptomycin and gentamicin affect predominantly the vestibular division. Neomycin, kanamycin and amikacin primarily affect auditory function. Tobramycin affects both equally.

b-The incidence of ototoxicity is directly related to the dose and duration of therapy.

c-Ototoxicity occurs more commonly when renal failure is present.

d-Simultaneous administration of the loop diuretic, ethacrynic acid, (and less likely furosemide) potentiates the ototoxic effects of aminoglycosides.

e-Elderly patients are more susceptible to ototoxicity.

f-Aminoglycosides cross the placenta and can cause eighth cranial nerve damage to the fetus.

2-Nephrotoxicity. It is usually reversible and may range from mild renal tubular dysfunction to acute tubular necrosis. Gentamicin and tobramycin are the most nephrotoxic. When renal failure of any degree is present, serum drug levels must be measured and dose adjusted as nephrotoxicity is dose-dependent.

3-Neuromuscular blockade. This may result with large doses and when combined with curariform drugs results in respiratory paralysis. This paralysis is usually reversible by calcium gluconate (given promptly) or neostigmine.

It is desirable when using higher doses of aminoglycosides to monitor drug concentrations in plasma by TDM.

Clinical uses:

1-Used most widely against gram-negative microbial infections especially when the organisms are resistant to the less toxic antibiotic and when there is suspicion of sepsis.

2-They are often used in combination with penicillins for treating certain infections to enhance permeability, facilitate entry and thus increase effectiveness of aminoglycosides. Penicillin also extend coverage to include gram-positive pathogens. However, penicillins and aminoglycosides must not be mixed in the same bottle because penicillin inactivates the aminoglycosides to a significant degree.

3-Due to their toxicity prolonged use should be restricted to the therapy of life threatening infections and when a less toxic agent is contraindicated or less effective.

STREPTOMYCIN

The antimicrobial activity of streptomycin is similar to other members but is **less active against aerobic gram-negative bacilli**.

Resistant microorganisms develop in most species rapidly which limits the current usefulness of streptomycin, and it is used generally in combination with other antimicrobial agents.

Clinical uses

l-Combined with penicillin in treatment of streptococcal endocarditis, and with tetracycline in treatment of plague and tularemia.

2-lts use in tuberculosis and other mycobacterial infections has been declined but it can be used in combination with others in treatment of extensive organ tuberculosis, acute tuberculous pneumonia, miliary dissemination or meningitis.

Streptomycin is administered by deep IM. injection, and this produces pain and tenderness at the injection site. It can also be given IV.

GENTAMICIN

Gentamicin is the aminoglycoside of first choice for the treatment of many serious gram-negative bacillary infections because of its low cost and reliable activity. However, emergence of resistant microorganisms in some hospitals has become a serious problem and may limit its future use.

Clinical uses

Gentamicin, I.M. or I.V., is empolyed mainly in serious gram-negative microbial infections. The therapeutic uses of gentamicin apply also to tobramycin, amikacin and netilmicin and they can be used interchangeably for the treatment of most of the following infections.

1-***Pneumonia caused by gram-negative bacilli***. An aminoglycoside given in combination with a β-lactam antibiotic is indicated.

2-***Meningitis caused by gram-negative organisms that are resistant to β-lactam antibiotics*** (given by intrathecal or intraventricular route).

3-***Pyelonephritis in seriously ill patients***. Given alone or in combination with a β-lactam antibiotic is very effective.

4-***Sepsis in immunocompromized patients***, particularly when infection with *P. aeruginosa* is suspected. An antipseudomonal penicillin plus an aminoglycoside is recommended.

5-***Peritonitis*** as a result of peritoneal dialysis.

6-***In some gram-positive infections as*** enterococcal endocarditis and selected cases of staphylococcal endocarditis, gentamicin in combination with a penicillin is effective.

7-***Topically*** gentamicin has been used for infected burns, wounds or skin lesions.

TOBRAMYCIN

The antimicrobial activity and pharmacological properties of tobramycin are very similar to gentamicin. It is more active than gentamicin against *Pseudomonas*.

Clinical uses:

Used in combination with antipseudomonal penicillin in the treatment of bacteremia, osteomyelitis and pneumonia caused by *Pseudomonas* species.

AMIKACIN

Amikacin is **unique in being resistant to the aminoglycoside-inactivating enzymes** and therefore it is active against most aerobic gram-negative bacilli including many strains of *Proteus, Pseudomonas and Enterobacter*.

Clinical uses:

Amikacin has become the preferred agent for initial treatment of serious nosocomial gram-negative bacillary infections in hospitals where gentamicin-and tobramycin-resistant organisms are prevalent.

NETILMICIN

Netilmicin shares many characters with gentamicin and tobramycin, but like amikacin it is not metabolized by most aminoglycoside inactivating enzymes. Consequently, netilmicin may be active against bacteria that are resistant to gentamicin and tobramycin.

Clinical uses:

The principal indication for netilmicin may be serious infections due to susceptible aerobic gram-negative bacilli.

KANAMYCIN

The use of kanamycin has **declined markedly** because it is most toxic and its spectrum of activity is limited compared with other aminoglycosides.

Clinical uses:

It may be used in combination with other drugs in treatment of tuberculosis in patients who harbor microorganisms that are resistant to the more commonly used agents.

NEOMYCIN

Neomycin is active against gram-positive and gram-negative bacteria. Strains of *Pseudomonas* and *Streptococci* are generally resistant.

Clinical uses

Neomycin is too toxic for parenteral use and is now limited to topical and oral uses.

l-Topically neomycin is used on infected surfaces of skin and mucous membranes or injected into joints, pleural cavity, tissue spaces or abscess cavities where infection is present.

2-Oral neomycin is used preoperative to reduce gut flora in preparation of bowel for surgery, and as an adjunct to the therapy of hepatic coma provided the renal function is normal. However, in hepatic coma lactulose is much less toxic and is used instead.