Pharmacology of Antibiotics

Definition:

Antibiotics may be informally defined as the subgroup of anti infectives that are derived from bacterial sources and are used to treat bacterial infections. Other classes of drugs, most notably the sulfonamides, may be effective antibacterials ***(Archer et al., 2001).***

Classifications:

Although there are several classification schemes for antibiotics, based on bacterial spectrum (broad versus narrow) or route of administration (injectable versus oral versus topical), or type of activity (bactericidal vs. bacteriostatic The most useful is based on chemical structure. Antibiotics within a structural class will generally show similar patterns of effectiveness, toxicity, and allergic potential ***(Gruchalla and Pirmohamed, 2006).***

Classification according to chemical stricture:

Beta-Lactam Antibiotics:

- Penicillins.
- Cephalosporins.
- Carbapenemes. (Imipenem)
- Monobactames. (Aztreonam)
- Beta-Lactamase Inhibiters :(Clavulanate potassium, Sulbactam sodium, Tazobactam).

Non-Beta-Lactam Antibiotics:

- Tetracyclines.
- Macrolides.

- Aminoglycosides.
- Quinolones.
- Glycopeptides.
- Sulfonamides.
- Cotrimoxazols.
- Polymyxine.
- Fusidic acid.
- Rifampicin.

(Fonacier, 2005).

Penicillins

The penicillins are the oldest class of antibiotics, and have a common chemical structure which they share with the cephalopsorins. The two groups are classed as the beta-lactam antibiotics, and are generally bacteriocidal that is, they kill bacteria rather than inhibiting growth ***(Critchley, 2003).***

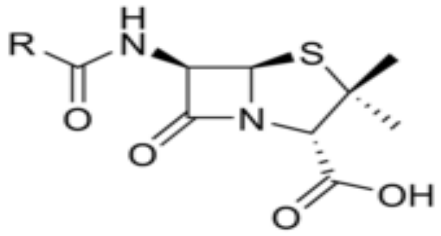

Fig. (1): Penicillin nucleus ***(Hugo et al., 2007).***

Penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are thus bactericidal they kill bacteria rather than inhibiting growth. Penicillins are

only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall and consequently they are inactive against organisms devoid of this structure as mycobacteria and fungi ***(Richard et al., 2006).***

The penicillins can be divided into 4 generations based on their spectrum of activity.

1st generation penicillins

1st generation penicillins are the naturally occurring penicillins, they work best against susceptible Gram-positive organisms and certain other organism such as Treponema pallidum, They are first line drugs for syphilis, and viridans streptococcal endocarditis.Members are penicillin (PCN) G and PCN V. Natural penicillins are quickly metabolized (if administered intravenously, the half-life about 30 minutes). to prolong blood levels it is given intermuscularly in a form that is slowly absorbed. Procaine can be injected with PCN G or benzathine penicillin. both of these combinations are absorbed slowly, so the doses do not have to be given as frequently ***(Gilbert et al., 2005).***

2nd Generation penicillins

2nd Generation penicillins were made to resist inactivation by penicillinase (beta-lactamase) from Methicillin-Sensitive Staphylococcus aureus (MSSA) and are stable when attacked by β-lactamases. They are not active against Gram negative organisms and are generally less active than penicillin against Gram-positives that do not produce b-lactamases.Their members include methicillin, nafcillin, dicloxacillin and oxacillin. When Staphylococcus aureus are said to be methicillin resistant, they are resistant to all second generation penicillins (in fact, to all beta-lactams), not just methicillin ***(Critchley, 2003).***

3rd Generation Penicillins

3rd Generation Penicillins, known as amino-penecillin, were made to treat some Gram negative organisms that do not make beta lactamases.They have some activity against Gram positives that lack penicillinase. Members include amoxicillin and ampicillin ***(Gilbert et al., 2005).***

4th Generation Penicillins

4th Generation Penicillins are big guns that were developed against nasty Gram negative pathogens like Pseudomonas. They have a broad spectrum of activity against many Gram-negative bacteria, but still can be inactivated by some beta-lactamases. They include mezlocillin and piperacillin (the ureido-penicillins), and carbenicillin and ticarcillin (carboxy-penicillins).The ureidopenicillins can be used against Enterococci and a number of other Gram-positives, but not S aureus ***(Critchley, 2003).***

Route of administration determined by stability of the drug to gastric acid and severity of infection, in ICUs the intravenous route is the commonly used route, distribution all over the body is good but penetration to Cerebrospinal Fluid (CSF) and bone is insufficient unless this sites are inflamed .Excretion is mainly by the kidneys so doses should be adjusted in renal failure. Probencid inhibits renal excretion of penicillins so increases blood levels ***(Gruchalla and Pirmohamed, 2006).***

Common adverse drug reactions (≥1% of patients) associated with use of the penicillins include: diarrhea, nausea, rash, urticaria, and/or super-infection (including candidiasis). Infrequent adverse effects (0.1-1% of patients) include: fever, vomiting, erythema, dermatitis,

angioedema, seizures (especially in epileptics) and/or pseudomembranous colitis ***(Salkind et al., 2001).***

Pain and inflammation at the injection site is also common for parenterally administered benzathine benzylpenicillin, benzylpenicillin, and to a lesser extent procaine benzylpenicillin ***(Atanskovie, 2005).***

Penicillin is still the most common cause of severe allergic drug reactions. Allergic reactions to any β-lactam antibiotic may occur in up to 10% of patients receiving that agent. Anaphylaxis will occur in approximately 0.01% of patients. There is about a 5% cross-sensitivity between penicillin-derivatives, cephalosporins and carbapenems. This risk warrants extreme caution with all β-lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any β-lactam antibiotic ***(Salkind et al., 2001).***

Cephalosporins

Cephalosporins and the closely related cephamycins and carbapenems, have the same mechanism of action as penicillins they contain a beta-lactam chemical structure. Consequently, there are patterns of cross-resistance and cross-allergenicity among the drugs in these classes. They are usually classified to four major groups based on their spectrum of activity ***(Stratton, 2003)***.

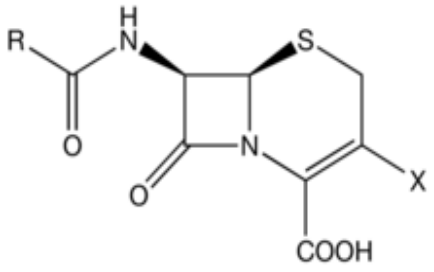

Fig. (2): Cephalosporin nucleus **(Pegler et al., 2007).**

There are lots of cephalosporins because it is very easy to modify their chemical structure. All the chemical names sound similar, so most practitioners use the distinctive brand names **(Gilbert et al., 2005).**

The cephalosporins can be divided into 4 generations based again on the spectrum of activity. Each successive generation is more active against Gram negatives and more resistant to b-lactamases. The trade off is that they lose activity against Gram positives ***(Niederman et al., 2001)***

1st generation cephalosporins

1st generation cephalosporins are good against methicillin sensitive S. aureus, streptococci and many Entero-bacteriaceae. Members include: Cephalexin (Keflex), Cefa-zolin (Ancef), Cephapirin (Cefadyl) and Cephalothin (Keflin) ***(Stratton, 2003).***

2nd Generation cephalosporins

2nd generation cephalosporins are more stable to Gram negative b-lactamase and less active against S. aureus. Members include: Cefuroxime (Ceftin [oral] and Zinacef), Cefotetan (Cefotan), and Cefoxitin (Mefoxin) ***(Niederman et al., 2001)***.

3rd Generation Cephalosporins

3rd generation cephalosporins have broader activity against Gram negatives.Members include: Cefdinir (Omnicef), Cefo-perazone (Cefobid), Ceftazidime (Fortam), and Ceftriaxone (Rocephin), and Cefotaxime (Claforan) ***(Stratton, 2003)***.

4th Generation Cephalosporins

4th Generation Cephalosporins are more resistant to destruction by chromosomal b-lactamases, but not completely resistant to the b-lactamases of Serratia, Enterobacter and Pseudomonas.Currently, there is one member, Cefepime (Maxipime) ***(Niederman et al., 2001)***.

Cephalosporins penetrate well into most body fluids and the Extra-Cellular Fluids (ECF) of most tissues, especially in the presence of inflammation (which enhances diffusion). However, only ceftriaxone, cefotaxime, ceftazidime, and cefepime achieve CSF levels sufficient to treat meningitis. All cephalosporins penetrate poorly into Intra-Cellular Fluid (ICF) and the vitreous humor ***(Gruchalla and Pirmohamed, 2006).***

Most cephalosporins are excreted primarily in urine. Dose adjustment is needed for these drugs in renal insufficiency. Cefoperazone and ceftriaxone, which have significant biliary excretion, do not require dose adjustment in renal insufficiency ***(Sherman, 2004).***

Several cephalopsorins and related compounds have been associated with Adverse effects like seizures. Cefmetazole, cefoperazone, cefotetan and ceftriaxone may be associated with a fall in prothrombin activity and coagulation abnormalities. Pseudomembranous colitis has been reported with cephalosporins and other broad spectrum antibiotics. Some drugs in this class may cause renal toxicity ***(Swartz and Morton, 2001).***

Carbapenems

They are synthetic B-lactam antibiotics, imipenems and meropenems are the only drugs of this group. They are active against penicillinase producing gram negative and positive organisms, anaerobes and P. aeruginosa so they play agreat role in empiric therapy. Imipenems are paired with cilastatin to protect from metabolism by renal dehydropeptidase but Meropenems do not undergo metabolism ***(Scott and Geoffrey, 2004).***

They penetrate into CSF with inflamed meninges. Meropenem is used for gram-negative bacillary meningitis; imipenem is not used in meningitis because it may cause seizures. Most seizures occur in patients

with CNS pathology or renal insufficiency who have received inappropriately high doses ***(Salkind et al., 2001).***

Monobactam: (Aztreonam)

Is a parenteral bactericidal antibiotic as active as ceftazidime against enterobacteriaceae and against P. aeruginosa. Aztreonam is not active against anaerobes. Unlike cephalosporins, gram-positive organisms are resistant. Aztreonamacts synergistically with amino-glycosides ***(Sherman, 2004).***

Because the metabolic products of aztreonam differ from those of other β-lactams, cross-hyper-sensitivity is unlikely. Thus the main use of aztreonam is severe aerobic gram-negative bacillary infections, including meningitis, in patients with serious β-lactam allergy who nevertheless require β-lactam therapy. Additional antibiotics are added to cover any suspected gram-positive cocci and anaerobes. The dose is reduced in renal failure ***(Gruchalla and Pirmohamed, 2006).***

Tetracyclines

Tetracyclines got their name because they share a chemical structure that has four rings. They are derived from a species of Streptomyces bacteria. Being broad-spectrum bacteriostatic agents, the tetracyclines may be effective against a wide variety of microorganisms, including rickettsia and ameobic parasites. ***(Stratton, 2003).***

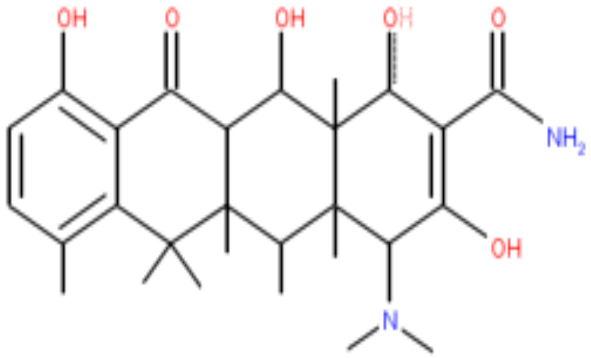

Fig. (3): Four ring structure of tetracyclines ***(Olson et al., 2006).***

Tetracyclines include: Naturally occurring that include, Tetracycline, Chlortetracycline, Oxytetracycline and Demeclocycline. 2): Semisynthetic (Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline and Rolitetracycline) ***(Bhattacharya, 2003).***

Tetracycline inhibits cell growth by inhibiting translation. It binds to the 16S part of the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome. The binding is reversible in nature ***(Parsi, 2001).***

Tetracyclines may be used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, intestines, and also gonorrhoea, especially in patients allergic to β-lactams and macrolides; however, their use for these indications is less popular than it once was due to widespread resistance development in the causative organisms ***(Bhattacharya, 2003).***

Their most common current use is in the treatment of moderately severe acne and rosacea (tetracycline, oxytetracycline, doxycycline or minocycline) ***(Stratton, 2003).***

About 60 to 80% of tetracyclineand ≥90% of doxycycline and minocycline are absorbed after oral administration. Because absorption is decreased by metallic cations (e.g., aluminum, calcium, magnesium, and iron), tetracyclines cannot be taken with preparations containing these

substances (e.g., antacids, many vitamin and mineral supplements). Food decreases absorption of tetracycline but not of doxycyclineor minocycline ***(Salkind et al., 2001).***

Minocycline is the only tetracycline that penetrates into tears and saliva in levels sufficient to eradicate the meningococcal carrier state. Tetracycline and minocycline are excreted primarily in the urine, may exacerbate azotemia, and should be avoided in patients with renal insufficiency ***(Richard et al., 2006).***

In renal failure, doxycycline is primarily excreted in the intestinal tract and requires no dose reduction. Tetracyclines cross the placenta to accumulate in fetal bones and teeth and are excreted in milk ***(Gruchalla and Pirmohamed, 2006).***

Adverse effects of tetracyclines includes Nausea, vomiting, and diarrhea and can cause Clostridium difficile colitis and Candida super-infections. Demeclocycline may cause increased photosensitivity. Minocycline may cause dizziness. Do not use tetracyclines in children under the age of eight, and specifically avoid during periods of tooth development. Oral tetracyclines bind to anions such as calcium and iron.Excessive blood levels from large doses or renal insufficiency may lead to fatal acute fatty degene-ration of the liver. Expired tetracycline should never be administered ***(Atanskovie, 2005).***

Macrolides

They are a group of drugs (typically antibiotics) whose activity stems from the presence of a macrolide ring a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. They includes Azithromycin (Zithromax), Dirithromycin (Dynabac), Erythromycin, Clarithromycin ***(Keicho and Kudoh, 2002).***

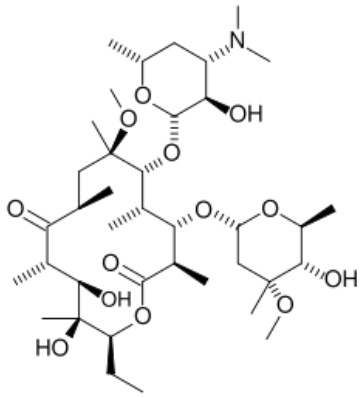

Fig (4): structure of clarithromycin (Biaxin) ***(Keicho and Kudoh, 2002).***

The mechanism of action of the macrolides is inhibition of bacterial protein biosynthesis by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyl tRNA. This action is mainly bacteriostatic, but can also be bactericidal in high concentrations. Macrolides tend to accumulate within leukocytes, and are therefore actually transported into the site of infection ***(Lopez-Boado and Rubin, 2008).***

Macrolide antibiotics are used to treat respiratory tract and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin. They cover not only beta-hemolytic streptococci, pneumococci, staphylococci and enterococci, but they also cover mycoplasma, mycobacteria, some rickettsia, and chlamydia ***(Keicho and Kudoh, 2002).***

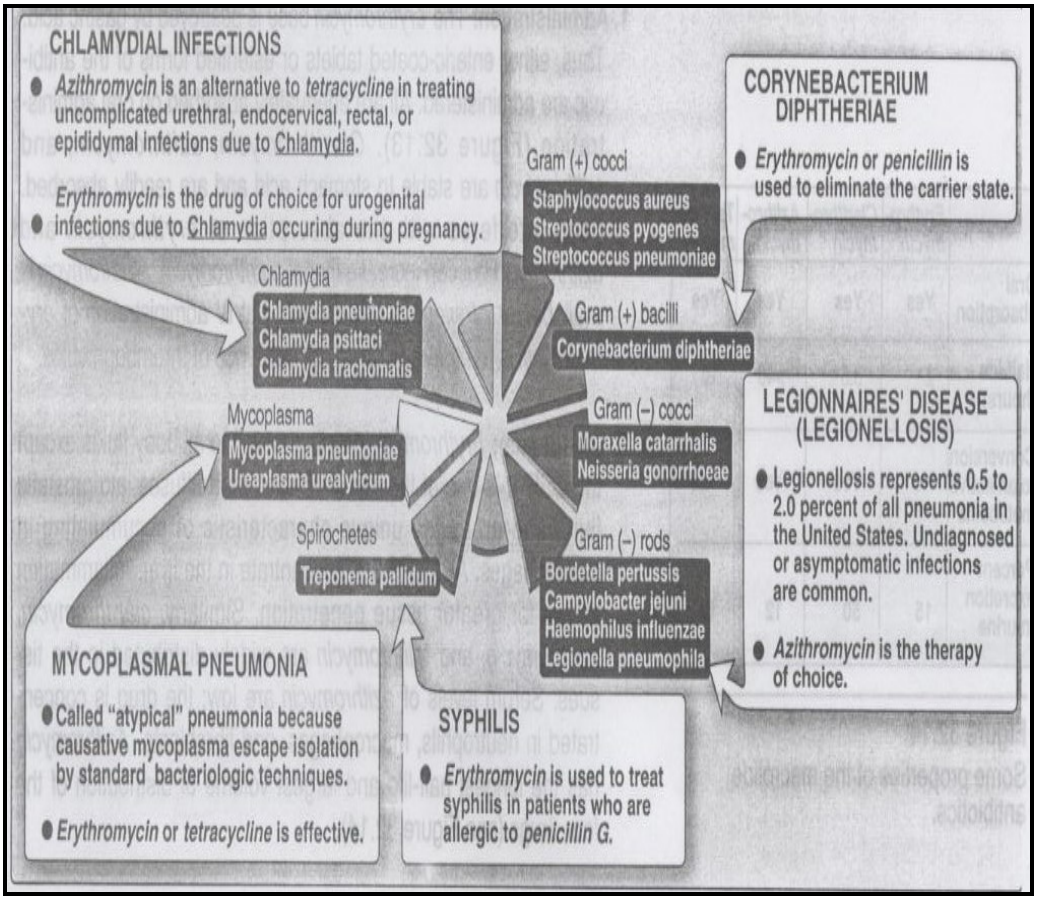

Fig. (5): Typical therapeutic applications of macrolides ***(Richard et al., 2006).***

Members of macrolides have different pharmacokinetics as they differ in their acid stability.

Erythromycin is easily inactivated by gastric acid; therefore, all orally-administered formulations are given as either enteric-coated or more-stable laxatives or esters, such as erythromycin ethylsuccinate ***(Maheshwai, 2007).***

On the other hand clarithromycin and azithromycin are acid-stable and can therefore be taken orally without being protected from gastric acids. Macrolides are very rapidly absorbed, and diffuses into most tissues and phagocytes by which they are transported to the site of infection and are released during active phagocytosis in large concentrations. The concentration of clarithromycin in the tissues can be

over 10 times higher than in plasma. Highest concentrations were found in liver and lung tissue ***(Malhotra et al. 2007).***

The commonest side effects are gastro-intestinal disturbances (nausea, vomiting, diarrhea, dyspepsia, abdominal pain and cramps). Side effects are more common and severe with erythromycin therapy. Azithromycin and clarithromycin have fewer gastrointestinal side effects than erythromycin.Allergic reactions, headache, taste disturbance, eosinophilia, reversible hearing loss, and hepatotoxicity are an infrequent side effects with all the macrolides so they must be avoided in severe liver disease ***(Bayarski and Yury, 2006).***

Aminoglycosides

They are bactericidal antibiotics, they bind to the 30S ribosome, thereby inhibiting bacterial protein synthesis.They are particularly useful for their effectiveness in treating P. aeruginosa infections ***(Carrat , 2004).***

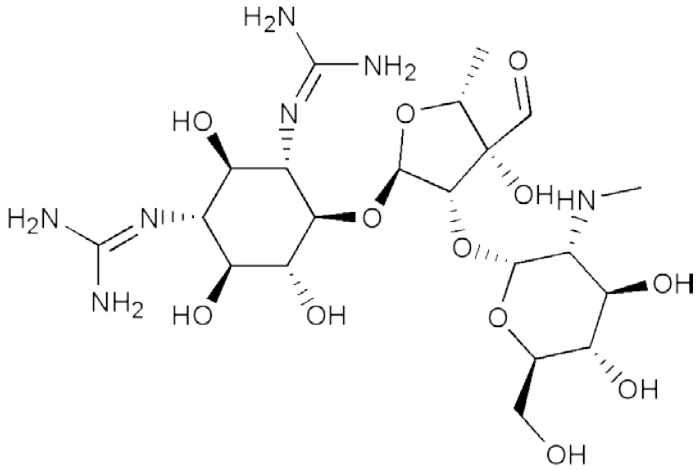

Fig. (6): Chemical structure of streptomycin (***Kingston and William, 2004)***.

Aminoglycosides are particularly useful for their effectiveness in treating Pseudomonas aeruginosa infections; Streptomycin is used to treat tuberculosis, and is sometimes used with a penicillin to treat enterococcal endocarditis ***(Critchley, 2003).***

Gentamicin, Tobramycin, and Amikacin are broad spectrum antibiotics. They are good against Gram negative rods and sometimes Staphylococcus aureus. Aminoglycosides and newer generation beta-lactams in combination are used to treat Pseudomonas. Overall, the aminoglycosides are toxic drugs. When possible, less toxic alternatives are used. Efficacy is concentration dependant ***(Critchley, 2003).***

Aminoglycosides are well absorbed from the peritoneum, pleural cavity, joints (and should never be instilled in these body cavities).They are distributed well into the ECF except for vitreous humor, CSF, respiratory secretions, and bile (particularly with biliary obstruction) ***(Simoes ,2004).***

Aminoglycosides are excreted by glomerular filtration and have a serum half-life of 2 to 3 hours, the half-life rises exponentially in renal insufficiency or in the elderly. Peak serum levels of at least 10 times the Minimum Inhibitory Concentration (MIC) are desirable ***(Atanskovie, 2005).***

This class of drugs causes kidney and ototoxicity. These problems can occur even with normal doses. Dosing should be based on renal function, with periodic testing of both kidney function and hearing ***(Ashworth, 2004).***

Fluroquinolones

The fluroquinolones are synthetic antibacterial agents, and not derived from bacteria. They are included here because they can be readily inter-changed with traditional antibiotics. An earlier, related class of antibacterial agents, the quinolones, were not well absorbed, and could be used only to treat urinary tract infections ***(Murray et al., 2002).***

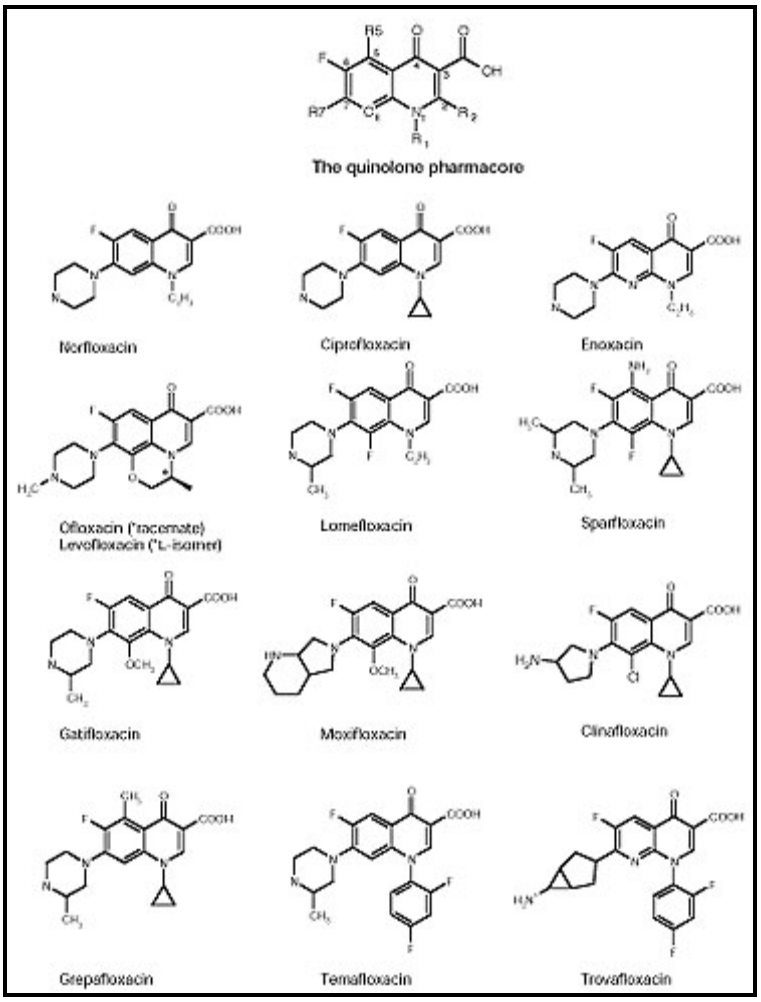

Fig. (7): The main structure and different members of fluoroquinolone group ***(Murray et al., 2002).***

Fluoroquinolones are bactericidal, broad-spectrum antimicrobials that act mainly by blocking Deoxyribonucleic Acid (DNA) gyrase; a bacterial enzyme that maintains the super twisted helical structure of DNA. The following organisms are very sensitive to these quinolones: Enteric gram-negative bacilli including: E. Coli, Proteus, Klebsiella (K), and Enterobacter; common GI pathogens including: Salmonella, Shigella, and Campylobacter ***(Salkind et al., 2001).***

An earlier, related class of antibacterial agents, the quinolones, were not well absorbed, and could be used only to treat Urinary Tract Infections (UTI).The fluroquinolones, which are based on the older group, are broad-spectrum bacteriocidal drugs that are chemically