CHEMOTHERAPEUTIC AGENTS-III

QUINOLONES & FLUOROQUINOLONES

R. MAITI,
SENIOR LECTURER IN PHARMACY

QUINOLONES

- First Quinolone , **Nalidixic acid** was isolated as a byproduct of the Chloroquine synthesis & mainly used for UTI.

  (**Bactericidal against most G-ve organisms except Pseudomonas but Less active against G+ ve organisms.**)
- **It acts by inhibiting DNA gyrase & is bactericidal.**
- **There is rapid development of resistance.**
- It is mainly used as a urinary antiseptic as a second line Drug .
- Nitrofurantoin is not given simultaneously as antagonism occurs .
- It is also given in diarrhea caused by Proteus , E. coli , Shigella & Salmonella infections.

FLUOROQUINOLONES

- **Introduction of Fluorinated 4- Quinolones**

Fluoroquinolone Members:

- **First generation FQs** -Ciprofloxacin, Norfloxacin, Ofloxacin , Pefloxacin.
- **Second generation FQs** - Lomefloxacin, Levofloxacin etc.
- **Third generation FQs** - Gemifloxacin, Gatifloxacin & Sparfloxacin.
- **4th generation FQs** - Moxifloxacin, Trovafloxacin , Alatrofloxacin & Finafloxacin.

FLUOROQUINOLONES

How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity
2. Improve Gram(+) activity

3. Acquire activity against anaerobes

FLUOROQUINOLONES

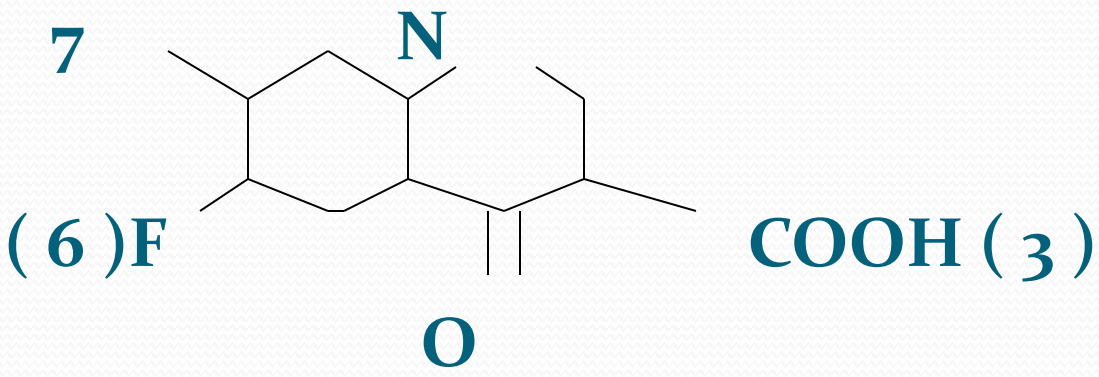
- Represents a particularly important therapeutic advancement because these agents have broad spectrum of AM activity & effective after oral administration for the treatment of wide variety of infectious diseases .
- Microbial resistance does not develop rapidly.

Chemistry :

- Quinolones contain a **carboxylic acid moiety at position-3** of the primary ring structure. Fluoroquinolones also contain a fluorine substituent at position- 6 & piperazine moiety at position – 7 & this is a breakthrough which confers high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability to these agents .

FLUOROQUINOLONES

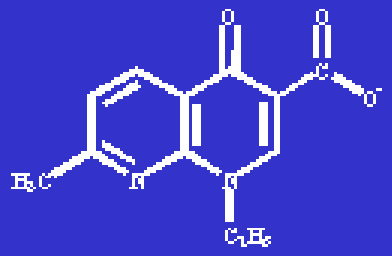
Structure:



FLUOROQUINOLONES

From nalidixic acid to the 1st fluoroquinolone (1 of 4)

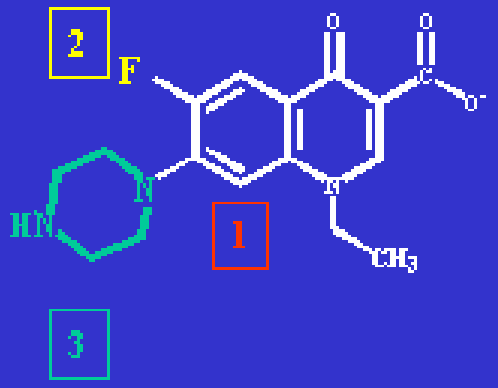
nalidixic acid



combine all 3 features *...

1978

norfloxacin *



broader Gram(-) activity
less protein binding (50%)
longer half-life (3-4h)

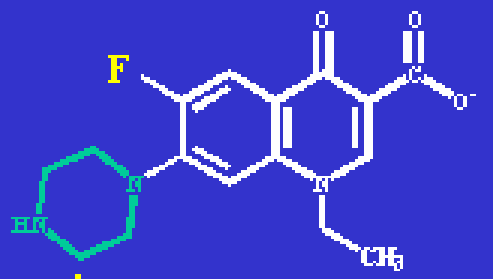
* Belgian patent 863,429, 1978 to Kyorin

* 6-fluoro-7-pyrimidino-quinoleine

FLUOROQUINOLONES

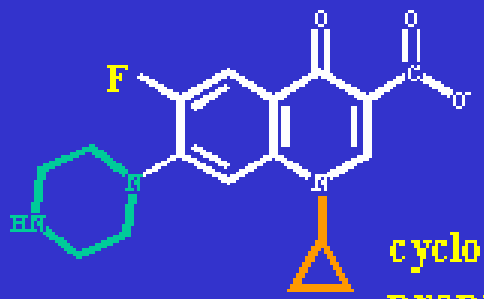
"1st generation" fluoroquinolones

norfloxacin

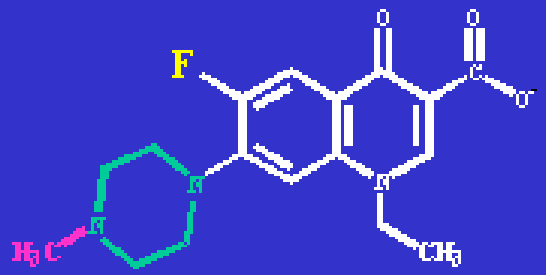


piperazine

ciprofloxacin

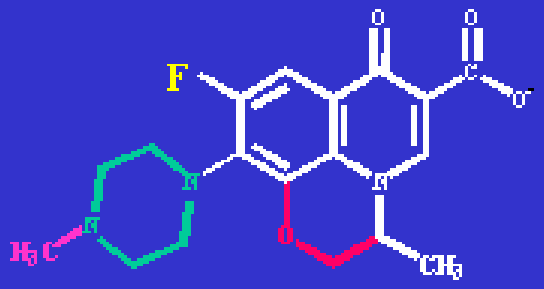


cyclo
propyl



methyl

pefloxacin



ofloxacin

morpholine

FLUOROQUINOLONES

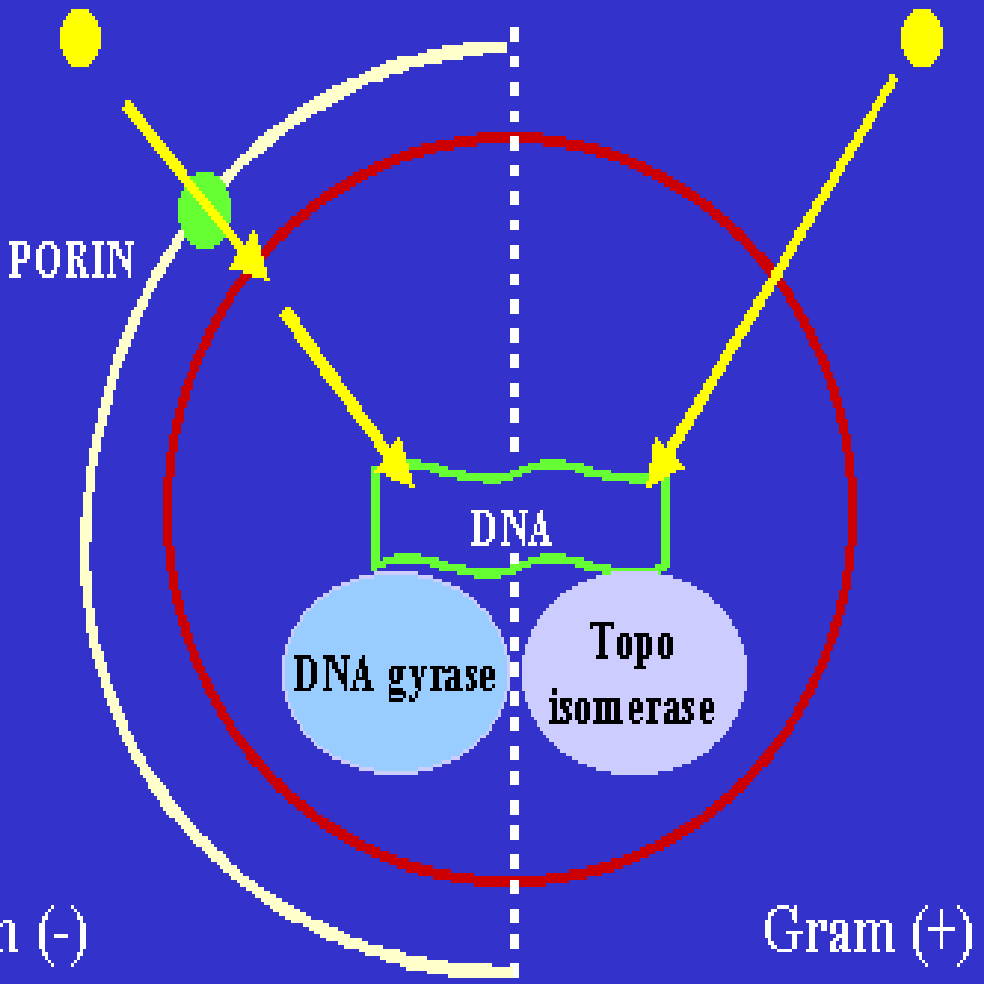
Mech. of action : Target is Bacterial **DNA Gyrase** & **Topoisomerase IV** enzyme.

- For most of the **G +ve** bact. e.g.- S. aureus, Topoisomerase IV is the primary enzyme inhibited by the FQs.
- In contrast many **G-ve** bacterial DNA Gyrase is the primary target of FQs.

Individual strand of double helical DNA must be separated to permit DNA replication & transcription.

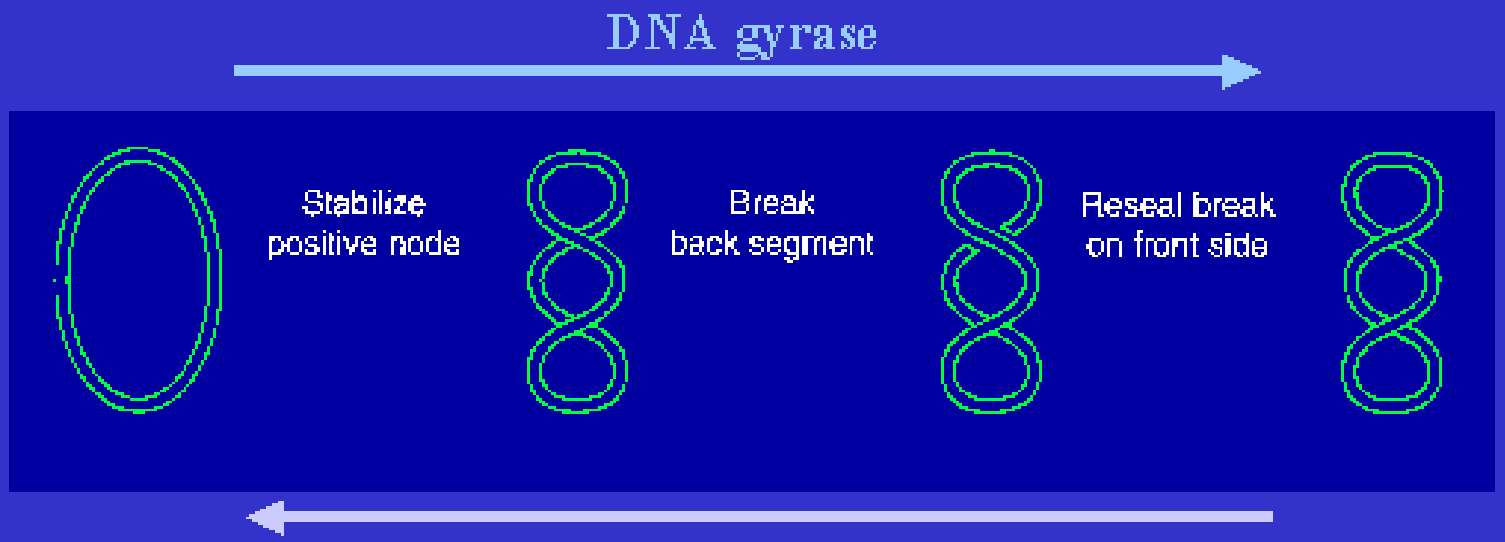
- DNA Gyrase is responsible for combating mechanical obstacle produced by overwind or excessive post-supercoiling of the DNA in front of the point of separation by continuous introduction of negative super coils into DNA.
- The **DNA Gyrase** of E.coli consists of two **subunits A & B** . The A subunit which carry out the strand cutting function of the gyrase is the site of action of the quinolone.

FLUOROQUINOLONES



FLUOROQUINOLONES

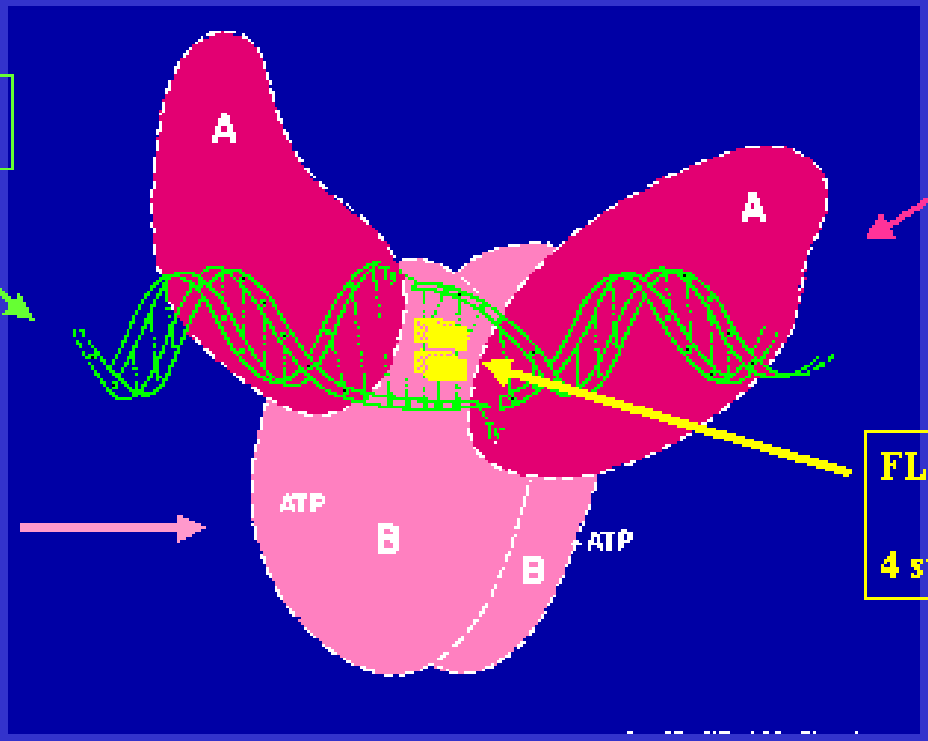
2 key enzymes in DNA replication:



bacterial DNA is supercoiled

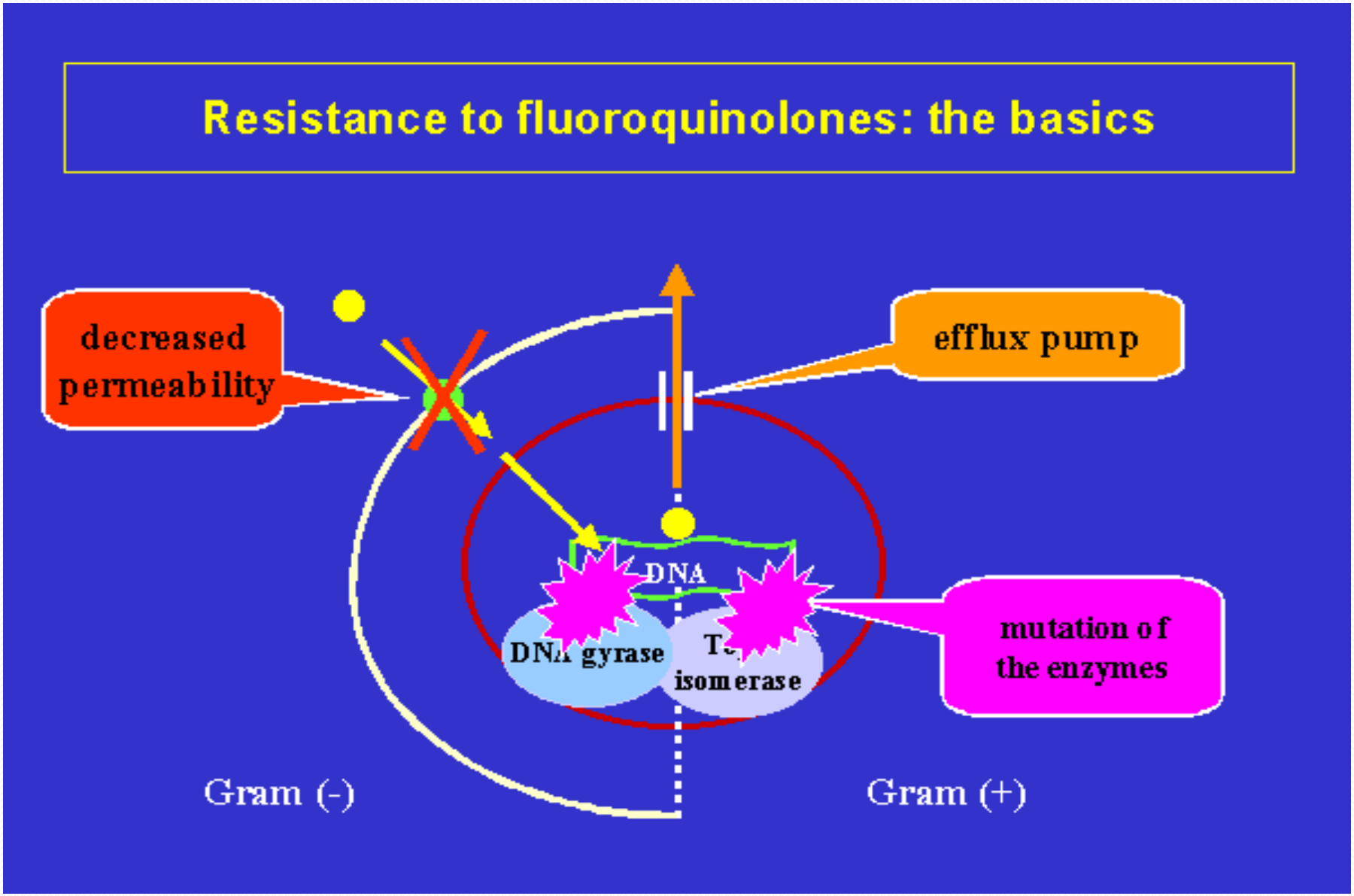
FLUOROQUINOLONES

Ternary complex
DNA - enzyme - fluoroquinolone



(Shen, in Quinolone Antimicrobial Agents, 1993)

FLUOROQUINOLONES



FLUOROQUINOLONES

Mutation of the gene that encode subunit- A polypeptide can cause resist.

Topoisomerase IV consists of 4subut. they separates interlinked daughter DNA molecules that are produced of DNA replication.(Eukaryotic cells have similar **type II** variant of **Topoisomerase** & quinolones suppress it in comparatively **much higher concentrations**).

Spectrum :

Bactericidal against **E.coli** ,**Salmonella Shigella**, **Enterobacter**, **Campylobactor** and **Neisseria, Klebsiella, V. cholera.**

(Ciproflox. is active against Pseudomonas aereug., Staphylococcus but not against Methicil resist. strains).

Some intracellular bacterias are also inhibited .e.g. – **Chlamydia** , **Mycoplasma**, **Legionella** , **Brucella** & **M.tuberculos.**

FLUOROQUINOLONES

Absorption ,Fate & Excretion :

- Quinolones are well absorbed after oral administration & distributed widely in body tissues.

(**Metal cations e.g.- Al , Mg , Ca, Fe & Zn form insoluble salts with Fluoroquinolones & inhibit the absorption**)

- **Doses** :
- **First generation FQs - Norfloxacin** – 400mg BD. , **Ciprofloxacin** – 500mg BD. , **Ofloxacin** - 200-400mg BD. **Pefloxacin.**
- **Second generation FQs** -(with additional fluoro substitutes further extending AM activity to Gram +ve cocci & anaerobes & having longer t ½) **Levofloxacin** - 500mg OD. , **Lomefloxacin**.
- **Third generation FQs - Gatifloxacin** -200-400mg OD , **Sparfloxacin** -400 mg 1st day then 200 mg OD,
- **4th generation FQs - Moxifloxacin** – 400 mg OD ,**Trovafloxacin, Alatrofloxacin** (Pro-drug for Trovaflox. Given I.V.) **& Finafloxacin.**

FLUOROQUINOLONES

- ✓ Most quinolones are cleared predominantly by the **kidney**

(doses must be adjusted for renal failure) except **Pefloxacin** & **Moxifloxacin** which are mainly metabolized by liver.

Therapeutic Uses :

1. **UTI** – Nalidixic acid only used in susceptible organisms. Fluoroquinolones are more potent & having much broad spectrum of AM activity.
2. **Prostatitis**
3. **Sexually Transmited Disease (STD):** (e.g.- Gonorrhoea , L. venereum, Chancroid but FQs lack activity against T. pallidum causing syphilis)- single oral dose of a Fluorq. e.g.-Ofloxacin , Ciprofloxacin is effective for sensitive strains of N. gonorrhoeae (but resistance led to Ceftriaxone as 1st choice)-Pelvic Inflammatory Disease (PID)

FLUOROQUINOLONES

4. Gastro- intestinal & abdominal infections:

- In **Traveller's diarrhoea**(by E. coli)
- **Shigellosis**
- **Cholera** (Norflox. is better than Tetracycline in ↓duration of diarrhoea.)
- **Enteric fever** by S. typhi (Cipro, Oflo & Levoflox.). It also clears chronic Fecal carriage.
- **Peritonitis** (in patients on peritoneal dialysis.)

5.Respiratory tract infections :

Poor activity against commonly Acquired pneumonia & bronchitis (newer Fluoroquinolones e.g.- Gatifloxacin have excellent activity against S.pneumonia ≡ β lact.). Other sensitive organisms for RT infections are H. infl., M. catarrh., S. aureus, M. pneum. & Legionella.

FLUOROQUINOLONES

6.Bone , Joint & Soft tissue infections:

- For chronic osteomylitis (Treatment need weeks to months) produced by S.aureus & G-ve rods.
- Diabetic foot infection
- In anaerobic infection it is given along with Metronidazole.

7. Other infections :

- Ciprofloxacin – prophylaxis of **Anthrax** (**It is in news for used as a weapon of Bioterrorism)** & Treatment of **Tularemia** .
- for **MDR** cases of **Tuberculosis** & for atypical mycobacterium infections caused by **Mycobacterium Avium** in AIDS patients.

FLUOROQUINOLONES

- **Pefloxacin**- methyl derivative of Norfloxacin, penetrates tissue better CSF conc. is better than other fluoroquinolones, therefore preferred drug for meningeal infections, also used for typhoid & gonorrhea .
- **Ofloxacin** - more potent than Ciprofloxacin for G +ve organisms, inhibits mycobact. tuberculosis & M. leprae & used as alternative in MDR regimen .
- **Levofloxacin** – levo - isomer of Ofloxacin , better activity against S. pneumoniae , also used in pyelonephritis, chronic bronchitis, sinusitis & other related infections of soft tissues. Can be administered just once a day.
- **Gatifloxacin** -spectrum same as other fluoroq.s , Gatifloxacin ophthal. sol. is the first FDA approved fluoroq.

- **Sparfloxacin** – difluorinated quinolone effective against G +ve bact., anaerobes & mycobacteria . Used in the treatment of pneumonia , chronic bronchitis , sinusitis etc. Causes QT –prolongation in ECG .

FLUOROQUINOLONES

- **Moxifloxacin** –having high activity against Strep. pneumoniae. & other G +ve organisms. Indicated mainly in bronchitis , pneumonia , sinusitis & otitis media , also used as eye drops.
- **Trovafloxacin** – It is more active than other fluoroq.s against strept.- pneumoniae & other G +ve bacteria. But due to its **hepatotoxicity** it is recommended only in life threatening infections).
- **Alatrofloxacin** – It is a pro-drug for Trovaflox. usually given I.V., both have an extended spectrum against anaerobes.
- **Finafloxacin** – More efficacious in tissues & body compartments having acidic pH with high safety profile & widest spectrum . Once daily dosing , oral / I.V. (undergoing phase III clinical trial).

FLUOROQUINOLONES

Adverse Effects :

- Quinol.s & Fluoroql. are generally well tolerated, most common **GI adverse reactions** are – mild nausea , vomiting and /or abdominal discomfort.
- **CNS-** mild headache & dizziness. Rarely hallucination, delirium & seizures can occur predominantly in patients who also are taking theophylline or NSAIDs simultaneously .
- Ciproflox. & Peflox. reduce the metabolism of theophylline, so toxicity can occur with elevated levels of theophylline.
- Rashes can occur including phototoxicity reactions.
- Achilles tendon rupture & tendinitis can occur rarely .
- All these agents can produce Arthropathy (joint erosions) & reversible arthralgia in several specises of animals & especially in children (therefore the use of quinol.s has been contra indicated in developing age & pregnancy).

FLUOROQUINOLONES

Miscellaneous Aspects:

- In some cases fluoroquinolones can be used where benefits may overweighs the risk of quinolone therapy in children.
- Leukopenia, Eosinophilia & mild elevation in Transaminases which may occur rarely.
- **QT prolongation** can occur with **Sparfloxacin** & to a lesser extent with Gatifloxacin & Moxifloxacin, therefore quinol.s should be used with caution in patients on class III (Amiodarone) & class IA (Quinidine, Procainamide) antiarrhythmics .
- Ciproflox + Amoxycil + Clavulinic acid has been shown to be effective as oral therapy for fever in low sensitive Patients with granulocytopenia.

THINK AGAIN