

# FLUOROQUINOLONES

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# Fluoroquinolones - Properties

- High Potency
- Expanded spectrum à Gm+ve, Gm-ve, Pseudomonas, Mycobacteria
- Better Tissue Penetration
- Good Tolerability
- Slow development of resistance
- Rapid Bactericidal Action
- Long Post Antibiotic Effect (PAE) à Ps., Staph., Strepto.
- Active à Beta-lactum aminoglycosides resistant bacteria
- Spares intestinal protective bacteria, anaerobes

# Fluoroquinolones

- Better than Quinolones like Nalidixic acid, Oxalinic acid
- **Classification :-**
- **I) First Generation Fluoroquinolones :-**
- Norfloxacin, Ciprofloxacin, Pefloxacin, Ofloxacin
- **II) Second Generation Fluoroquinolones :**
- Levofloxacin, Lomefloxacin, Sparfloxacin, Gatifloxacin, Moxifloxacin

# Fluoroquinolones – Mechanism of Action

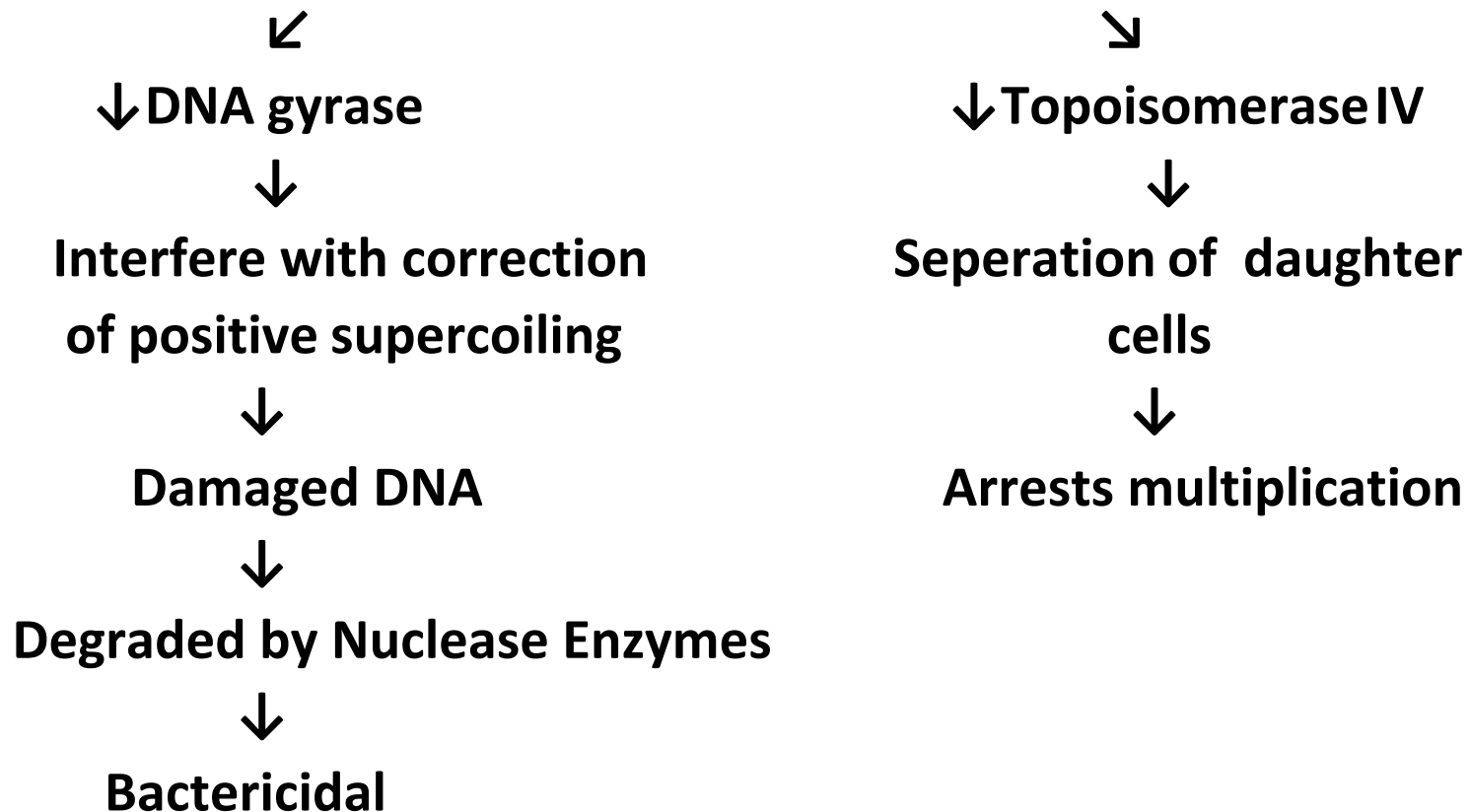
- Are bactericidal
- Inhibit bacterial DNA - gyrase enzyme and Topoisomerase IV enzyme → inhibit bacterial DNA synthesis
- **During DNA replication**, DNA gyrase enzyme continuously introduce negative supercoiling thereby opposing the positive supercoiling of the DNA. Fluoroquinolones inhibit DNA replication.
- **In human cells**, instead of DNA gyrase, they have Topoisomerase II, which require 1000 folds higher conc. of fluoroquinolones, hence not inhibited in human by therapeutic dose.

# Fluoroquinolones – Mechanism of Action

- **Topoisomerase IV is essential for separation of the daughter cells following replication**
- **Fluoroquinolones inhibit Topoisomerase IV and block the separation of daughter cells**
- **Thereby, fluoroquinolones inhibit the Gm +ve bacteria by inhibiting Topoisomerase IV enzyme, while it inhibits Gm-ve bacteria by suppressing DNA gyrase enzyme**
- **Bacteria with damaged DNA are formed which are degraded by nuclease enzymes. Thus, FQs produce bactericidal action.**

# Fluoroquinolones – Mechanism of Action

## Fluoroquinolones (FQs)



# Fluoroquinolones - USES

- **1) UTIs** : Very effective in sensitive & resistant cases.  
Norfloxacin : 400mg BD for 5-10 days
- **2) Typhoid (Enteric Fever)** : Ciprofloxacin / Ofloxacin are DOC .  
Ciprofloxacin : 500mg BD -10 days, Ofloxacin : 200mg BD for 10 days. Also eradicates carrier state
- **3) Diarrhoea** : due to Shighella, Salmonella, E.coli & Campylobacter
- **4) RTIs** : due to H. Influenzae, Legionella & Mycoplasma causing Pneumonia. Levofloxacin, gatifloxacin are highly effective as once daily dose for 7-10 days
- **5)Chanchroid** : Ciprofloxacin 500mg BD for 3 days

# Fluoroquinolones - USES

- **6) Bone, joint, soft tissue & intra- abdominal infections :** Osteomyelitis & Joint infections reqd. Prolong treatment.
- **7) Tuberculosis :** Ciprofloxacin, sparfloxacin are used in MDR-T.B. Also used in atypical mycobacterial infections
- **8) Bacterial Prostatitis & Cervicitis :** FQs are useful. Chlamydial urethritis & cervicitis also responds to Cipr or sparfloxacin
- **9) Anthrax :** Ciprofloxacin is DOC. Also useful for prophylaxis
- **10) Eye Infections :** Cipro/Ofloxacin/Gatifloxacin eye drops
- **11) Neutropenic Patients :** FQs used in prophylaxis
- **12) Meningococcal carrier state :** FQs eradicate carrier state
- **13) Gm –ve septicaemia :** FQs + III generation Cephalosporins/ Aminoglycosides



# Fluoroquinolones –Adverse Effects

- **1) N,V,Gastric discomfort**, diarrhoea & skin rashes
- **2) Tendinitis** causing tendons rupture
- **3) Arthrosis / Arthropathy in children** à causing damage to the growing cartilage of the joints à C/I in children below 18 yrs of age
- **4) CNS stimulation** precipitating convulsions, headache, dizziness and insomnia
- **5) Epileptogenic seizures** precipitated in pts taking NSAIDs, Theophylline
- **6) Prolongation of QTc interval** with Levofloxacin, Gatifloxacin
- **7) Phototoxicity**

# Ciprofloxacin - Contraindicated

- 1) Pregnancy
- 2) Children below 18 yrs due to risk of Arthropathy / Arthrosis
- 3) Pts with prolonged QTc interval & receiving drugs like Mefloquine, Erythromycin, Class I & II antiarrhythmic drugs
- 4) FQs + Theophylline due to increase risk of theophylline CNS toxicity
- 5) Concurrent use of Calcium, iron, decrease FQs absorption
- 6) Dose adjustment in renal failure

# Pharmacotherapy of Typhoid (Enteric ) Fever

## 1) Causative Organisms :- (Gm -ve)

\*\* Salmonella Typhi

\*\* Salmonella Paratyphii

## 2) Incubation Period : 3 – 21 days

## 3) Route of Transmission :

\* Contaminated food / water, \* Close contact with infected person

\* chronic carriers

## 4) Diagnosis : Widal Test

## 5) Drugs Treatment :

(i) Fluoroquinolones :- Ciprofloxacin, Ofloxacin, Gatifloxacin

(ii ) 3<sup>rd</sup> Generation Cephalosporins :- Ceftriaxone, Cefaperazone, Cefixime, Cefpodoxime Proxetil, Cefdinir

(iii) Aminopenicillins :- Amoxycillin, Ampicillin

(iv) Chloramphenicol

(V) Cotrimoxazole

# Typhoid Fever Treatment (Contd...)

- **4) Clinical signs & symptoms :-**

- \* High Grade Fever, Abdominal Pain

- **5 ) Early Physical Findings :-**

- Rose spots on trunk, chest; Hepatosplenomegaly,  
Epistaxis, Tachycardia High Grade Fever (38.s – 41.5C),  
Chills, headache, anorexia, cough, weakness, sore throat,  
dizziness, muscle pain

- **6) Late complications :-** Intestinal perforation & Bleeding Life threatening à require surgical intervention)

# Typhoid Fever Treatment (Contd...)

## (I) Fluoroquinolones :-

I) **Ciprofloxacin** : Drug of First choice

- **Advantages of Ciprofloxacin :**

- 1) Highly sensitive to S.Typhi & paratyphi strains
- 2) Bactericidal
- 3) Inhibits bacterial DNA synthesis by inhibiting DNA gyrase & Topoisomerase IV enzymes
- 4) Fever subsides within 4-5 days (Quick Defervescence)
- 5) Early symptoms resolution
- 6) Narrow chances of relapse & complications
- 7) High biliary, intestinal mucosal concentration
- 8) Prevention of carrier state

# Typhoid Fever Treatment (Contd...)

- **Ciprofloxacin (Contd...)**
- 9) Good Penetration into infected cells
- 10) High eradication rate of 92%
- **Dose :** 1) 500-750 mg BD \* 10 days orally  
2) 200mg I.V. Infusion B.D. , then, 100 mg I.V. Infusion B.D.  
3) **Typhoid Carrier state** – Ciprofloxacin 750 mg BD \* 4-8 weeks

# Typhoid Fever Treatment (Contd...)

- **(II) Third Generation Cephalosporins :-**
- Drugs used are :-
- **(a) Parenterally** : Ceftriaxone, Cefoperazone
- **(b) Orally** : Cefixime, Cefpodoxime proxedil, cefdinir
- **CEFTRIAXONE :- Advantages are :-**
- \* Fastest acting bactericidal
- \* All isolates including MDR are sensitive
- \* Early abatement of symptoms ; \* Early defervescence
- \* Prevents relapse ; \* Prevents carrier state
- \* Bactericidal effect by inhibiting bacterial cell wall synthesis
- \* Greater cure rate
- \* Preferred in children, where Ciprofloxacin is contraindicated

# Typhoid Fever Treatment (Contd...)

- **CEFTRIAXONE :- Disadvantages are :-**
- \* Costly / Expensive treatment
- \* Only given by Parenteral route – hence, needs to be hospitalized
- \* Restricted use when other antibiotics are not preferred
- **Dose of Ceftriaxone in Typhoid fever :-**
- **(1) Adults :- 4.0 Gm I.V. Once a day for 2 days, then, 2.0 Gm I.V. Till 2 days after fever subsides.**
- **(2) Children :- 75 mg / kg/ day I.V.**



# Typhoid Fever Treatment (Contd...)

- III) Ampicillin / Amoxycillin :- Disadvantages are :-
- Nowadays, not dependable
- Infrequently used, when other drugs cannot be given
- Development of multidrug resistance
- Response is slow
- Defervescence takes 7-10 days
- In sensitive persons :- used as an alternative drug, is cheap and safe.

# Typhoid Fever Treatment (Contd...)

- **(IV) Chloramphenicol : Advantages are :-**
  - No longer used as a first line therapy
  - Used in S.Typhi strain sensitive pts
  - Rapid clinical improvement in 3-4 days
  - Defervescence in 4-7 days ; Cheap
- **Disadvantages of Chloramphenicol :-**
  - Bacteriostatic ; Relapse occurs in 10 %
  - Does not prevent or Cure - carrier state
  - Increase incidence of resistance to it
- **Dose : (1) Adults : 500mg 6 hrly till fever subsides, then, 250 mg 6 hrly for 7 days.**
- **(2) Children : 50 mg/ kg / day**

# Typhoid Fever Treatment (Contd...)

- (V) Co-trimoxazole :-
- Alternative in patients not tolerating fluoroquinolones
- Nowadays, resistance have developed
- In sensitive strains of S. Typhi it is useful
- **Dose** :- Cotrimoxazole DS Tabs BD for 2 weeks
- (Sulfomethoxazole 800 mg + Trimethoprim 160 mg )
- Eradicates carrier state with 12 weeks treatment , provided gall bladder is not involved

## Pharmacotherapy of Typhoid (Enteric) Fever

- Typhoid fever is also known as 'Enteric Fever'
- Causative organism : Salmonella Typhii
- Sign & Symptoms : High Grade fever, chills, anorexia, nausea, bodyache, red spots on trunk & abdomen, intestinal perforation & intragastric bleeding on prolonged disease
- Diagnosis : Widal Test after 5 days of fever, Typhi – DoT- Test
- Typhoid fever Positive if Salmonella Typhii Titres are high
- Treatment includes :-
- Bed rest, Liquid diet
- Antipyretic, analgesic, H-2 Blockers/Proton –pump inhibitors
- Fluoroquinolones, 3<sup>rd</sup> Generation cephalosporins, Chloramphenicol, Ampicillin/amoxicillin, Cotrimoxazole

## Pharmacotherapy of Typhoid (Enteric) Fever

### (I) Fluoroquinolones :-

**Drug of First Choice (DOC)**

### Examples :-

**Ciprofloxacin, Ofloxacin, Gatifloxacin,  
Moxifloxacin, Levofloxacin**

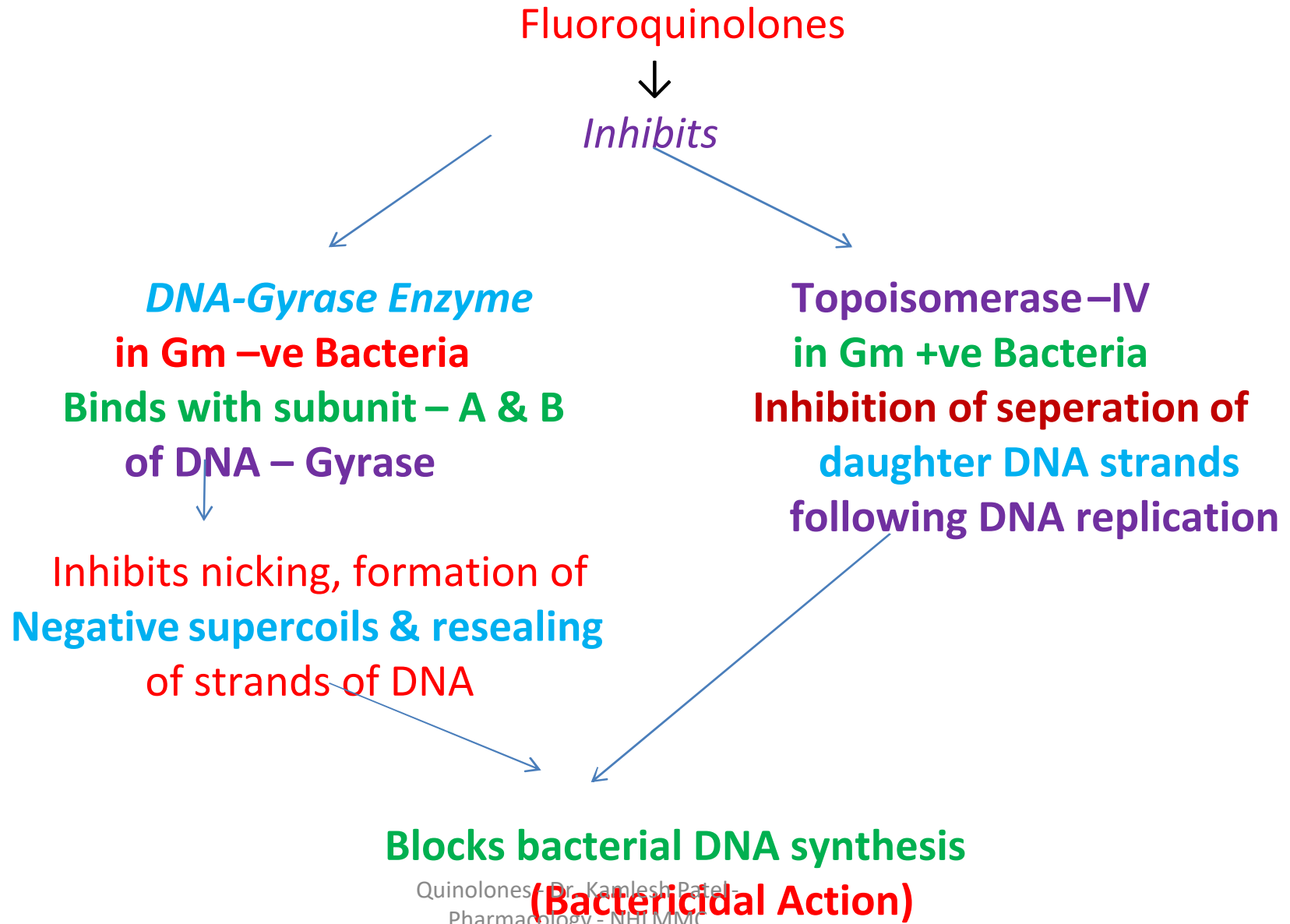
**Available as tablets, IV infusion**

**Are Bactericidal**

**Acts** by inhibiting bacterial DNA synthesis

**Higher tissue penetration in lungs, intestines,  
urinary tract, prostate in males, bones**

# Fluoroquinolones - MOA



# Fluoroquinolones

## Advantages in Typhoid fever:-

- 1) Drug of First Choice
- 2) Given by both oral & parenteral route
- 3) Early abatement of symptoms
- 4) Produces early defervescence of fever (within 72 hrs)
- 5) Produces 98-100% bacteriological & clinical cure rates
- 6) Eradicates carrier state (Ciprofloxacin 750 mg BD \* 8 weeks)
- 7) Less chances of recurrent & relapses
- 8) Switch-on Therapy from parenteral to oral therapy ,once pt. can tolerate oral food & medicines
- 9) Oral Dose : Ciprofloxacin 500 – 750 mg BD \* 10-14 days

# Fluoroquinolones

## *Disadvantages of Fluoroquinolones in typhoid fever :-*

- 1) **Contraidicated in children below 12 yrs à due to risk of tendinitis & arthrosis (Damage to the joint cartilages)**
- 2) **Cannot be given during pregnancy**
- 3) **Increases toxicity of aminophylline when concurantly administered**



# Cephalosporins in Typhoid Fever

- **Third Generation Cephalosporins effective :-**
- **I) Parenteral :- Ceftriaxone, Cefoperazone, Cefotaxime**
- **II) Oral :- Cefixime, Cefpodoxime Proxetil, Cefdinir**

## 1) Ceftriaxone in Typhoid Fever:-

- **3rd generation parenteral cephalosporin**
- **Longer plasma t<sub>1/2</sub> life - 8 hrs**
- **Once or twice daily dosing**
- **Good penetration into tissues, CSF**
- **Effective DOC in Typhoid fever, multi-resistant typhoid fever in adults and children**
- **Acts by inhibiting Bacterial Cell wall synthesis**
- **Is Bactericidal**

# Cephalosporins in Typhoid fever

- Advantages of Ceftriaxone in Typhoid fever:-
- **DOC** in children where **Fluoroquinolones** are **contraindicated**
- **Rapid onset of action**
- **Early abatement of symptoms**
- **Early defervescence of fever**
- **Nearly 100% Bacteriological & Clinical cure rate**
- **Eradicates carrier state à Less chances of relapse and recurrences**
- **Well tolerated, less side effects**
- Dosage of Ceftriaxone in Typhoid Fever :-
- 1) Adults :- 4 G i.v. daily for 2 days , followed by 2 G / Day till 2 days after fever subsides
- 2) Children :- 75mg/Kg /day

## Cephalosporins in Typhoid fever

- 2) Cefoperazone :
- Dose : 1-3 g i.m / i.v 8 – 12 hrly
- Risk of Disulfiram – like reaction with alcohol, thrombocytopenia
- 3) Cefotaxime :
- As an alternative to Ceftriaxone in Typhoid fever
- Pl  $t_{1/2}$  is 1 hr , but metabolized to active metabolite - hence 12 hrly dosing
- Bactericidal and inhibits bacterial cell wall synthesis
- Dose :- 1-2 gm i.v 12 hrly in adults; 50-100 mg/kg/day in children

## **Ampicillin / Amoxicillin/ Chloramphenicol/Cotrimoxazole**

- **In the past used to treat typhoid fever**
- **Currently, S. Typhii has developed resistant to all the above drugs à Not used routinely**
- **Drawbacks of all above drugs in Typhoid fever are :-**
- **Slow onset of action, takes longer time to cure pt**
- **Slower abatement of symptoms**
- **Longer time for defervescence of fever**
- **Not effective in carrier state**
- **Less bacterial & clinical cure rates**
- **Higher relapse rate**
- **Development of resistance**
- **Poorly tolerated , increase risk of side effects**
- **Different dosage pattern**