Nalidixic acid is predecessor to all FQ.

FLUOROQUINOLONES

→ use has been closely tied to C. difficile & ...

The unfavourable effects of FQ on "INDUCTION & SPREAD" of bac. resistance are sometimes reffered to as "collateral damage" ⇕ unintended damage, injuries or death

a term - associ c̄ 3rd gen. ceph

MOA

Top-II affinity (cipro) significant or more prominent in gram -ve → P. aeruginosa

enters through porin

- ⊖ → DNA gyrase (Topoiso-II) → Relax. of supercoiled DNA → DNA strand breakage.
- ⊖ → Topoiso IV → chromosome stabilization ⊖ → separation of newly replic DNA

mecham → (more prominent in g +ve) → strep. pneumonia (moxi cipro favour this) due to high affinity for IV Topo.

⇒ Bactericidal & activity more pronounced c̄ ↑se 30 fold the MIC to serum conc of bacter

Spectrum AND Applications

Ciprofloxacin is DOC for post exposure [redacted] prophylaxis and treatment of ANTHRAX "commonly affect animals → transm to human" (skin affected)

★ Doxycycline — alternative

+ cocci

- St. pneumoniae
- Bacillus anthracis

Resistant Resp. Trac infec ★ - levo. effective in treating infec. unresponsive to β-lactam antibio. such as AUGMENTIN

★ CIPRO. — NOT DOC for pneumonia or sinusitis becoz it has week activi against St. pneumonia — (causative agent)

UTI ⟹

cipro & levo — for both compli & uncomp. UTI

-ve rods

- Enterobacter sp.
- E. coli
- H. influenza
- K. pneumoniae.
- Legionella pneumophila
- Proteus mirabilis
- P. aeruginosa
- Serratia marcesens
- Shigella sp.

★ - Levo & MOXI are know as "Resp. FQ" due to activity eg. strep. pneu ⇓ CAP

Anaerobic infec

MOXI — activity notable.
∴ infec. that can occur where there is less O₂ supply causing infec & gas gangrene and diff. abscess

UTI: cipro is effective in treating acute diarrhoeal illness due to enteric pathogen

NOT USED FOR:

- S. Aureus
- [redacted] Enterococci
- Syphilis
- N. gonorrhea

} due to resistance.

cipro treat uncomplic. case of gonorrhea PO OD

- Anaerobic microorg.
- Atypical organ.
- Other: M. Tuberculosis

CLINICALLY USEFUL FQ

Norfloxacin

- poor oral B.A
- short $t_{1/2}$
- effective for Non-sys. infec. such as UTIs, prostitis & infec. diarrhea.

Ciprofloxa.

- effeciv for sys. infec caused by g-ve
- 80 B.A so oral & IV both are used.

BID — Therapeutic uses — OD (extended-release)

- P. aeruginosa
- Cystic fibrosis
- Traveler's diarrhea (E. coli)
- Typhoid fever (salmonella)
- TB (2nd line)

PTTC

Levofloxac.

- L-isomer of ofloxa.

Therapeutic

- prostitis
- skin infec.
- CAP
- HAP
- 100% B.A
- OD

Moxiflox.

(UTI crossed out)

- Active against g+ve & anaero.
- poor activ. against P. aerug.
- NOT indicat. for UTI becoz they don't concen. in urine.
- longest $t_{1/2}$

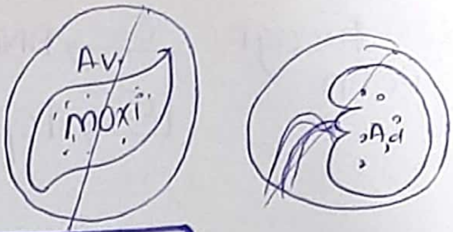
RESISTANCE

cross-resistance occur among FQ.

gyro = Top-II
ParC = Top-IV

Altered target
- Chromos. mutation in genes (gyrA or ParC)
- Both Topois - II & IV undergoes mutation.

↓se Accum.
- ↓ porin channel
- ↑ efflux pump.



KINECTICS

Absorp

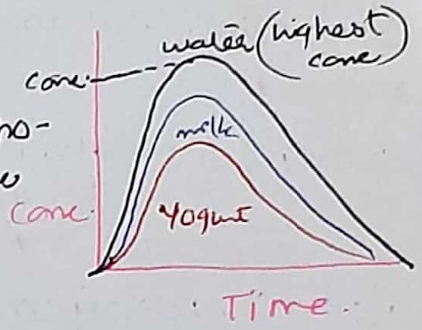
- 35-70% - norfloxa
- 80-99% other
- IV and opth of MIC - aavail
- (Sucralfates, Al-mg Antacids or dietary supp (Iron or Zn) ↓se absorb. including Ca^{2+} & other divalent ion.

Distribu

- Wide distri all over body fluids & tissues
- Bone & urin high levels except MOXI
- CSF = low
- macrop, polymorphonuclear leukocytes

Elimination

- Renal
- Dose adj requ. [redacted]
- MOXI → Liver



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ADRs

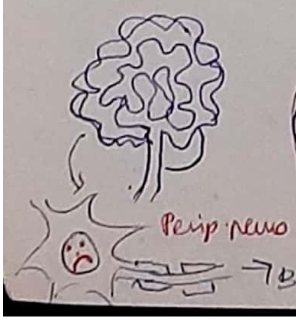
- N/V/D
- Headache
- Dizziness
- light headedness
- caution in CNS disorders

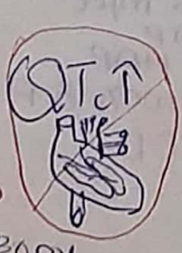
- Peripheral neuropathy
- Glucose dysregulation
- Phototoxicity
- Prolong QTc interval

pt's are advised to use sunscreen & avoid excess exposure to light.

- Articular cartilage erosion (arthropathy)
  - PG
  - Lactat
  - Age < 18
- Tendinitis & Tendon rupture.

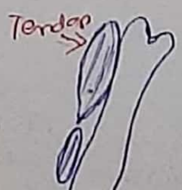
Drug inter
↓
- ↑ serum Theophylline (inhibiting metab)
- ↑se Warfarin caffeine & cyclosporin serum level
- ↑ TCEW

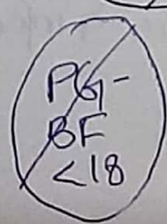




Glucose ↑↓

Thiazid: Hyperglycemia





SULFONAMIDES

They're rarely prescribed alone except in developing countries (low cost, efficacy)

MOA

Microorganism | Human & mice

Pteridine precursor + PABA —(Sulfamethoxazole (Sulfa Drugs) ⊖)→ Dihydrofolic acid —(Trimethoprim ⊖; NADPH → 2NADP; DHFR)→ THF → A.A synthesis; Purine synth; Thymidine synth

Dihydropteroate Synthetase; Glutamate

(for PABA – due to struct. similarity)

"Sulfa drug compete for DHPS enzyme" — These drugs are bacteriostatic.

Spectrum / T. uses

- Enterobacteriaceae in UTI
- Nocardia infec. (gram +ve) (affect lungs, brain & skin from soil & water) esp ē weak immune.
- Toxoplasmosis (Parasitic infec. – swollen lymph node around neck and inflamm of lungs, heart, muscl) (eating uncooked, or contam. food; from Pg mother to child) (sulfadiazine + DHFR inhibitor) Pyrimethamine
- antimalarial (Sulfadoxine + pyrimethamine) 500 + 25 mg [Fansidar – Brand; Non-immune pt: 1 tab once a week.]

Resistance

- [redacted] Bac. that obtain folate from their environment are resistant
- Cross-resis occur in this group
- Altered DHPS
- ↓se cellular permeability
- ↑se Produc. of natural PABA

KINETICS

Remember green highlights for ADRs

Absorption

All absorp after oral adm. excep. Sulfasalazine (reserve for treatment of bowel disease — inflammatory ulcerative colitis)

Local intestin flora act on Sulfasalazine → Sulfapyridine (used in RA) → Toxic for slow acetylators; 5-aminosalicyl. → anti-inflamm. effect

Topically (silver sulfadiazine or mafenide) → Burns → ↓se Burn also sepsis

S.S is preffered over mafenide (Painful, produce Acid-base disturbance).

Distrib

- Bound to serum (albumin)
- Binding dep on Pka (↓ pka = ↑ binding)
- Can enter
  - CSF
  - placenta
  - Fetal tissues

(PG) (BF) as excreted in B. milk

Metab.

acetylated & conjug in liver → metabolites are toxic if precipitat neutral or acidic pH → cause crystalluria (stone formation) → Kidney damage.

Excretion

- excreted via kidney (GFR + secretion) (Dose adj req. in renal disease).
- in breast milk

(AD)

ADRs

MM-W

- **Crystalluria** → Adequate hydration and alkalinization of urine prevent this nephrotoxic condition.
- **Hypersensitivity** (most common adr) → Rashes, edema, SJS
- **Hematopoietic disturban.** → Occur in pt ē G6PD deficiency; Granulocytopenia; ↓platelet: Thrombocytop.; Types: agranulocytosis, aplastic anemia
- **Kernicterus** (kernicterus) → Occur in newborns. Sulfa drug displace bilirubin from bind. sites on albumin. Bilirubin enter CSF Becoz BBB is not develop fully → Brain damage
- **DI** warfarin and MTX increase by same MOA / vision
- **Contraindication** — Newborn; < 2 month; PG; methenamin co-adm [As crystalluria can occur]

TRIMETHOPRIM

- Potent inhibitor of DHFR — spectrum similar to sulfa drugs.
- Mostly use in combin. form — cotrimoxazole.

MOA

Trimethoprim ⊖

DHF ——————→ THF —⊖→ A.A / purine / pyrimidine

↑ DHFR (reduction rex)

TMP is more active on Bac. red. (Bac. red. has more affinity for TMP)

Spectrum

- Similar to sulfonamides
- More potent (20–50X) than sulfa.
- Use alone only in treatment of → UTIs, Bacterial prostitis (NOT DOC) — FQ are preffe[redacted]

Resistance

- Altered DHFR
- Efflux pump
- ↓se permeability

KINECTICS

- Rapid abs. after oral adm.
- High conc. achieve in acidic prostitic & vaginal fluid becoz it is a week base. (prostitis)
- Wide distri. including CSF
- Undergoes O-demethylation but 60–80% is excreted in urine unchanged (UTI)

ADRs

FOLIC ACID DEFICIENCY

- megaloblastic anemia — (large, abnormal, immature RBCs)
- leukopenia — Low WBCs
- granulocytopenia ——— ↓ peripheral blood granulocytes 0.5–10⁹/L ↓ neutrophils, basophils, eosinophils [Esp in PG and P[s ē poor diet]

ADRs (F.A deficiency ↓se) by ⇓ simultaneous adm. of folinic acid ↓ which doesn't enter bac.

★ - Pus & tissue extract antagonize sulf. action

★ - Agranulocytosis: absolute neutrophils count (ANC) is less than 100 neutrophils/µL — may cause septicemia or sepsis — blood poisoning by bacteria. Sepsis may progress to septic shock → death

★ aplastic anemia: body stop producing enough new blood cell → infections can occur

Malarial prophylaxis - Single dose of 3 tab.

COTRIMOXAZOLE

Synergistic activity ← (Trimethoprim + Sulfamethoxazole) → Both have similar $t_{1/2}$ — Bactericidal

(1:5) – 1 = TMP – as it is potent

MOA

Sulfamethoxa → Inhibit incorpor. of PABA into Dihydrofolic acid precursors

Trimethoprim → • Prevent reduction of DHF ⟶ THF

Spectrum + Appln.

MRSA | FQ = ineffec

Coli – effective for community acquired MRSA skin & soft-tissue infec.

Respiratory infections

coli. effective against H. influenza

• coli is alternative for Legionella pneumophila

Pneumocystis Jiro. pneumonia (PCP)

– Common opportunistic infec complicating AIDS.

coli. is most effective

– Prophylaxis ē coli. is recom. for HIV-infec. pts ē fewer than 200 CD4⁺ cell/ml.

Gram +ve cocci
S. aureus
(+) bacilli
Listeria monocyt.
–ve rods
E. coli
H. influenza
Legionella pneumophila
Proteus mirabi
S. typhi
Shigella sp.

Other
P. jirovecii
Toxoplasm. gondii

Listeriosis
Ampicl or cotrimox. is effective in treating septicemia and mening. caused by L. monocyto. – (also causes food poisoning)

Prostatic & UT Infections
• Trimetho. concentrate in prostatic & vaginal fluid making it effective in treating these infec.
• chronic UTI responds to COTRI.

GI infections
COTRI ⇄ Shigellosis → intestinal infec. ↳ Diarrhea ↳ Abd. pain
Non-Typhoid salmonel
Arrangemt of carrier S. Typhi

• Toxoplasmosis in AIDS

Resistance

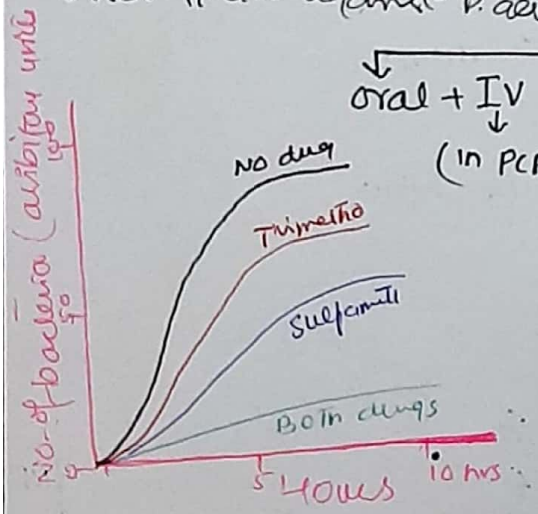
Bac. Rarely develop resistance becaz it requires resis to both the drugs

HOWEVER resis is shown in E. coli and MRSA.

• Not effective against P. aerog.

KINECTICS

Oral + IV (in PCP) → concentrate in acidic enviro of prostatic & vag. fluid → cross BBB → Excreted in urine.



Bac – E. coli

ADRS

Skin rex • N/V
• Glossitis ← inflam of tongue
– stomatitis
• Hyperkalemia = high doses
• Megaloblastic anemia, leukopenia ↓se by folinic acid co-adm
• Thrombocytopen. ← in
• Hemolytic anemia (G6PD deficiency)

DI
• ↑se PT when co-ad ē warfarin
• ↑se serum conc. of Phenytoin (↑ $t_{1/2}$)
• MTX ↑se due to displacemt from albumin

Do watch lecture on Pharmaco-study youtube

UTI Antiseptic/Antimicro:

1) E-coli – Most common causative agent
2) S. Saprophyticus — 2nd most common

- UTI — common in child bearing age of women.
- (Cotri, Quinolon or following agents can be used)

1) Cotrimoxa } 3 day
2) FQ (cipro/levo) } Both therapies are considered superior.

METHAMINE

Mechanism

At pH 5.5 or less Methamine ↓ decompose Formaldehyde + Ammonia (Toxic to bac.).

- Metha. develop c̄ weak acid (mandelic or hippuric acid) to keep urine acidic
- Antacid ($NaHCO_3$) should be avoided.

Spectrum

- Use to reduce the frequency of UTI
- NOT recommended for routine use in order to avoid catheter-asso. UTI
- NOT used to treat Pyelonephritis (upper UTI)
- NOT used for proteus sp (which is urea-splitting bacteria → [Alkalinize the urine]

Kinetics

- Orally adm
- Ammonium ion is metab by liver urea to form so metham is CI in pt c̄ Hepatic insuff as ammonia can accumulate
- Distribute widely But doesn't decomp at pH 7.4 → NO system toxic
- CI the co-adm c̄ sulfonamides ↙ ↑ risk of crystalluria ↘ mutual[redacted] antagonism

ADRs

- GI distress
- albuminuria, hematuria & rashes at high doses
- Methamine mandelate is CI in renal insuff becoz mandelic acid precipi

$$\text{Methamine} \xrightarrow[4NH_4^+]{6H_2O} 6\,\text{Formaldehyde}$$

HCHO ⇓ Kill bac.

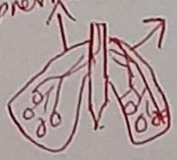
urea = $CO(NH_2)_2$

NITROFURANTOIN

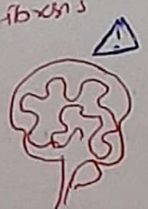
(pulmonary SE; ē cost)

- Sensitive bac. reduces the drug to highly active interm. ⇓ inhibit various enzymes ⇓ That damages bacteria
- Against E.coli But other g-ve UTI causing agents are resistants
- g +ve cocci (S. saprophyticus) susceptible.
- Hemolytic anemia in G6PD deficient pt.
- GI disturb.
- acute pneumonitis
- neurolog. prob
- interstitial pulmonary fibrosis

acute pneumonitis



interstitial pulmonary fibrosis



H. Anemia

G6PD

methamine [Hepatic imp, Sulfonamides] ← CI → [renal impair, 38 weeks or more pregnant] NF

G6PD = a defect in G6PD cause RBCs breakdown, opposite to normal function