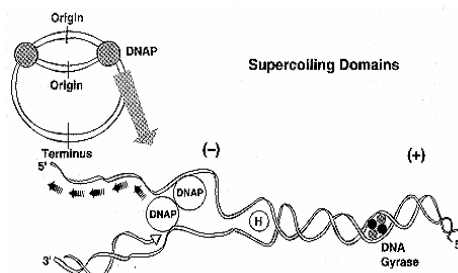


Lecture Outline

- Quinolones
- Trimethoprim/Sulfamethoxazole
- Miscellaneous antimicrobials -
 - Metronidazole
 - Daptomycin
- Cases

Quinolones - Mechanism of Action



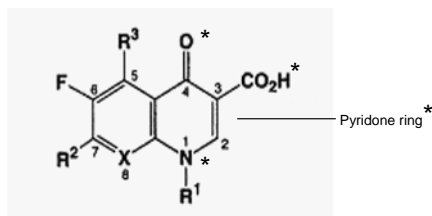
Quinolones

- Bactericidal broad spectrum antibiotics
- Increasingly used because of their relative safety, their availability both orally and parenterally and their favorable pharmacokinetics
- There is increasing concern about the emergence of resistance to these agents

Quinolones - Mechanism of Action

- Quinolones are bactericidal. They inhibit bacterial DNA synthesis in several ways causing rapid cell death
- Quinolones bind the DNA-DNA gyrase (topoisomerase II) complex blocking further DNA replication

Quinolone Structure



* Required for antibacterial activity

Quinolones - Mechanism of Action

- Quinolones block topoisomerase IV interfering with separation of interlocked (concatenated), replicated DNA molecules
- There appear to be additional sites of quinolone action that are as yet not well characterized

Quinolones - Antibacterial Spectrum

- 1st generation (quinolones - nalidixic acid): limited to Gram negative enteric bacteria (UTIs)
- 2nd generation (fluoroquinolones - norfloxacin, ciprofloxacin): improved Gram negative coverage with activity against *S. aureus* (systemic infections), *Pseudomonas* and also against *B. anthracis*
 - Addition of fluorine and piperazine derivative

Bacterial Resistance to Quinolones (2)

- Resistance can emerge during therapy - especially with *S. aureus* or *P. aeruginosa*. A single mutation is sufficient to cause resistance.
- Resistance is chromosomal rather than plasmid-mediated.
- Mutations occur in the genes for DNA gyrase (topoisomerase type II)

Quinolones - Antibacterial Spectrum

- 3rd generation (fluoroquinolones - levofloxacin): Improved activity against Gram positives *e.g.* staphylococci and pneumococci, also has activity against mycoplasma and legionella (systemic infections)
 - Longer half life
 - Increased structural complexity, greater antimicrobial spectrum but also increase in some toxicity
- Gatifloxacin and moxifloxacin are two newer agents with extended half-lives and enhanced Gram positive activity

Bacterial Resistance to Quinolones (3)

- Mutations also occur in the genes for topoisomerase IV
 - Appear to be primary site for *S. pneumoniae* and other Gram positives
- Active efflux system
 - Present in both Gram positive and negative bacteria

Bacterial Resistance to Quinolones (1)

- In the past ten years there has been a dramatic increase in the frequency of resistance to quinolones
- Selective antibiotic pressure and horizontal spread of strains appears to be responsible
- Use of quinolones in animal feed has also contributed to increasing resistance among some bacterial species

Quinolones - Pharmacokinetics (1)

- Well absorbed orally - bioavailability of $\geq 50\%$
- Some fluoroquinolones are available parenterally
- Excellent tissue distribution - Conc'ns in kidney, prostate, lung and bile usually > serum. Conc'ns in bone, CSF < serum.
- Quinolones also achieve high intracellular conc'ns (e.g. PMNs)

Quinolones - Pharmacokinetics (2)

- Elimination - Most are eliminated by the kidneys, although some are eliminated by the liver
- Drug interactions - decreased oral absorption following coadministration of metal cations

Indications for the Use of Quinolones (1)

- Empiric therapy of community-acquired pneumonia in selected settings
- Oral therapy of complicated urinary tract or respiratory tract infections
- Oral therapy of serious infections such as osteomyelitis, pneumonia or soft tissue infections

Quinolones - Toxicity (1)

- Quinolones are among the most well tolerated antimicrobial agents
- Gastrointestinal, CNS symptoms can occur
- Allergic reactions - rash, urticaria, drug fever
- Photosensitivity (additional fluorine or chloride at position 8 increases the incidence)

Indications for the Use of Quinolones (2)

- Treatment of sexually transmitted diseases: gonorrhea, chancroid, chlamydial urethritis
- Empiric therapy of travelers diarrhea
- Therapy for multidrug-resistant tuberculosis

Quinolones - Toxicity (2)

- Liver function abnormalities - usually mild, rare fatalities recently reported following treatment with trovafloxacin
- Joint symptoms - arthralgias, joint swelling, tendonitis
 - Cartilage damage

Quinolones - cautionary tales!

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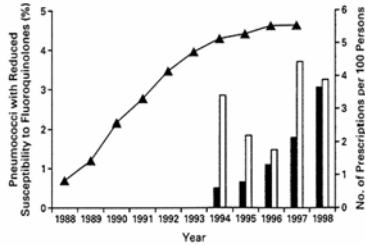


QUINOLONE-RESISTANT *CAMPYLOBACTER JEJUNI* INFECTIONS
IN MINNESOTA, 1992-1998

DECREASED SUSCEPTIBILITY OF *STREPTOCOCCUS PNEUMONIAE*
TO FLUOROQUINOLONES IN CANADA

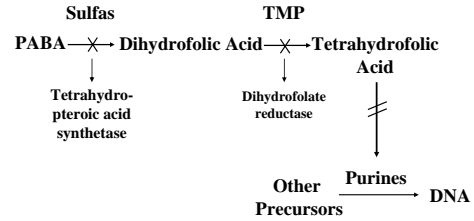
DANNY K. CHEN, M.D., ALLISON MCGEE, M.D., JOYCE C. DE AZAVEDO, PH.D., AND DONALD E. LOW, M.D.,
FOR THE CANADIAN BACTERIAL SURVEILLANCE NETWORK*

Quinolones - Cautionary Tales!



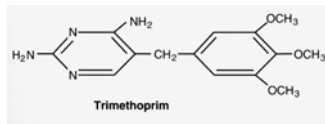
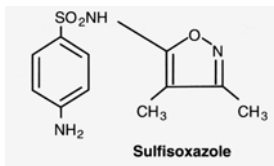
Chen et al. *NEJM* 341:233,1999

Trimethoprim-Sulfamethoxazole: Mechanism of Action



Zimmer & Mayer, Mandell ID

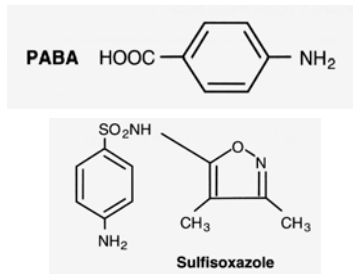
Trimethoprim-Sulfamethoxazole



Trimethoprim-Sulfamethoxazole: Mechanism of Action

- Sequential interference with folic acid synthesis results in bacterial synergism often with bactericidal activity
- Sulfonamides are structural analogues of para-amino benzoic acid (PABA), competitively inhibiting synthesis of dihydrofolic acid
- Trimethoprim is an analogue of the pteridine portion of dihydrofolic acid inhibiting synthesis of tetrahydrofolic acid

Trimethoprim-Sulfamethoxazole



Trimethoprim-Sulfamethoxazole Resistance

- Resistance is reduced because of the sequential interference with steps involved in folic acid synthesis
- Sulfas: decreased permeability (plasmid-mediated), increased production of PABA
- TMP: synthesis of DHFR with decreased affinity for TMP (plasmid-mediated), overproduction of DHFR
- Resistance to both TMP and SMZ has been increasing.

Trimethoprim-Sulfamethoxazole Pharmacology

- Combination antibiotic with 1:5 ratio of TMP to SMZ achieves a serum ratio of 1:20
- Available both orally or parenterally
- Both agents are well distributed achieving good levels in the lungs, kidneys, biliary tree and the central nervous system
- Both are partially metabolized in the liver and are excreted in the urine.
- The serum half-life is 9-11h, however it is prolonged in subjects with renal insufficiency

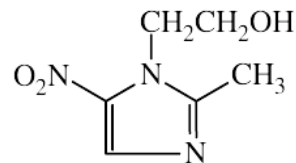
Trimethoprim-Sulfamethoxazole Indications for Use

- Urinary tract infections
- Prostatitis
- Treatment of *Pneumocystis carinii* infection
- Treatment of diarrheal illnesses due to salmonella, shigella and enterotoxigenic *E. coli*
- Treatment of upper and lower respiratory infections caused by susceptible organisms
- Treatment of selected infections caused by susceptible pathogens - *B. cepacia*, nocardia,

Trimethoprim-Sulfamethoxazole Spectrum of Activity

- Excellent broad spectrum activity against a diversity of microorganisms
- Gram negatives: *E. coli*, klebsiella, proteus, salmonella, shigella, vibrio, *B. cepacia*, *H. influenzae*, *Neisseria spp.*
- Gram positives: staphylococci, streptococci, listeria, not enterococci
- Miscellaneous: pneumocystis, nocardia, chlamydia

Metronidazole



Mechanism of action: accumulation of short-lived intermediate compounds or free radicals that damage DNA and other cellular macromolecules

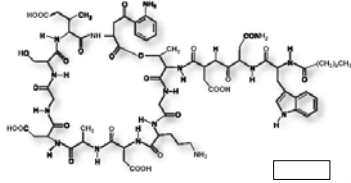
Trimethoprim-Sulfamethoxazole Toxicity

- Hypersensitivity reactions: rash, fever
- GI symptoms: nausea, vomiting diarrhea
- Rare: hepatitis, megaloblastic anemia, increased serum creatinine
- Toxicity from TMP-SMZ including fever, rashes, Stevens Johnson syndrome, is dramatically increased in subjects with AIDS. The reason for this is unclear.

Metronidazole

- Spectrum of activity:
 - Bactericidal against anaerobes especially *Bacteroides fragilis*, clostridia species. No aerobic activity
 - Active against trichomonas, giardia, entamoeba,
- T1/2 8h well distributed including CNS
- Multiple means of administration - oral, parenteral, rectal or vaginal
- Clearance delayed by hepatic but not renal dysfunction.
- Toxicity - generally well tolerated
 - GI - nausea vomiting
 - Disulfiram effect with alcohol
 - CNS (rare)

Daptomycin



Mechanism of action: bactericidal lipopeptide that disrupts the cytoplasmic membrane by insertion of the tail in a calcium dependent reaction

Clinical Scenarios

A 44 year old male presents with fever, chills, cough and chest pain. His cough is nonproductive. On physical his respiratory rate is 33, you hear bibasilar rales and his chest X-ray reveals bilateral lower lobe infiltrates. His laboratory studies are not helpful. You treat him with what?

Does it matter that the incidence of penicillin resistance Among pneumococci in the community is 15%?

Daptomycin

- Spectrum of activity:
 - Bactericidal against Gram positive bacteria including staphylococci, streptococci and enterococci especially vancomycin-resistant strains
- T1/2 8-9h
- Mode of administration - parenteral only
- Clearance primarily by the kidney
- Indications:
 - Resistant Gram positive bacterial infections
 - Endocarditis, skin soft tissue infections, not pulmonary infections
- Toxicity - generally well tolerated
 - Concern about myopathy but not seen to date

Clinical Scenarios

Despite three days of your therapy he fails to improve. You take a more detailed history and discover he is at risk for HIV. Does this alter your initial therapy?

You treat him with trimethoprim sulfamethoxazole and steroids in addition to your fluoroquinolone and he slowly improves however seven days later he develops a rash.

Clinical Scenarios

A 58 year old diabetic with chronic renal disease develops a soft tissue infection that spreads to involve the underlying bone. Biopsy and culture of the involved tissue reveals a mixed infection of the bone with *K. pneumoniae* and *Bacteroides spp.* He tells you that he had an anaphylactic reaction to penicillin 10 years ago.



Clinical Scenarios

A 30 year old medical student is about to go to a rural area of Mexico for a two month primary care elective. He is concerned about the possibility of contracting an infectious diarrhea while there and decides to take some antibiotic with him. What would be a good choice for empiric therapy of a diarrheal illness in this setting?

Clinical Scenarios

A 75-year old male is found to have enterococcal endocarditis. One week into therapy his isolate is discovered to be both ampicillin and vancomycin resistant. What should he be treated with at this point?