Nitrofurantoin

• For UTIs (since 1953)
• Not for systemic infections
  • Absorbed but very rapidly cleared by kidneys, 25-40% unmodified
  • Plasma half-life only ~20min; serum concentration extremely low
  • Becomes more active under acidic pH
  • Not for pyelonephritis because drug concentration in those tissues insufficient
• Active against *E. coli* (one of the most common UTI pathogens)
  • Not active against many other Gram-: *Proteus, Klebsiella, Pseudomonas, Enterobacter, Serratia*
• Active against some Gram+: *Enterococci* (including VRE; nosocomial), *Staph. aureus, Staph. saprophyticus*
Nitrofurantoin: mechanism of action

- Nitrofurantoin activated by bacterial flavoproteins, becomes reactive and damages ribosomal proteins, DNA, other macromolecules involved in metabolism, cell wall synthesis
  - Similar end effect to metronidazole, but no cross-resistance
  - Not particularly susceptible to resistance developing, transferable resistance rarely observed
- Bactericidal at concentrations reached in urine
Nitrofurantoin: adverse effects

- GI effects (dose related): nausea, vomiting

- Rare but serious adverse effects (<<1%)
  - Peripheral neuropathy
  - Hepatotoxicity
  - Pulmonary toxicity, fibrosis with long-term use: lung disease
  - Affects glutathione reductase activity: in Glucose-6-Phosphate Dehydrogenase (G6PD) deficient patients (cannot regulate glutathione levels), risk of hemolytic anemia

- Contraindicated in pregnancy (>38 weeks gestation) and neonates due to risk of hemolytic anemia resulting from neonates’ immature blood cells

- Renally cleared, so contraindicated in renal insufficiency

- Carcinogenicity observed in small animals, mutagenic in bacteria; but the clinical significance not known
Nitrofurantoin forms

- Taken with food increases absorption
- Microcrystalline: Furadantin ®
- Macrocristalline: Macrobid ®, Macrodantin ®
  - Absorbed more slowly, so less GI distress
• Fosfomycin competes PEP from MurA and prevents it from initiating peptidoglycan synthesis: prevents formation of N-acetylmuramic acid
Fosfomycin: another UTI drug

- MurA enzyme (a.k.a. UDP-N-acetylglucosamine enolpyruvyl transferase) normally would generate N-acetylmurameric acid from N-acetylglucosamine by adding enolpyruvate.
Fosfomycin mimics PEP, which would normally be ligated to UDP-N-acetylglucosamine by MurA (a.k.a. UDP-N-acetylglucosamine enolpyruvyl transferase)
Fosfomycin

- Monurol ®
- Uncomplicated UTI
- Broad activity against Gram+ and Gram-
  - Some *Enterobacteriaceae*: *E. coli*, *Proteus*, *Citrobacter*
    - Including some ESBL-producing *E. coli*
  - *Enterococci*: *E. faecalis*
- Bactericidal
- Single 3gm dose.
- Excreted to urine (and some to feces)
- Relatively low frequency of adverse reactions
- Resistance emerges readily: transporter protein needed for fosfomycin uptake mutates so drug doesn’t get taken up