Intro to Bacteria & Miscellaneous drugs for UTIs, Incontinence, BPH, and Acne

PHRM 203
Allison Beale
Goal of antibacterial chemotherapy

- Selective or Relative toxicity
  - Attack targets that are:
    - Unique to the pathogen
      - Cell wall
    - Similar, but not identical to the host
      - Protein synthesis
    - Shared by the host, but with a different level of importance
      - Folic acid and DNA nucleotide synthesis
Bacteria are Prokaryotes

• Genetics and Reproduction
  – No “nucleus”
    • Just a discrete area, the “nucleoid”
  – Reproduction is usually “asexual”
    • Always binary fission, but some swap DNA
    • Some form spores (e.g., \textit{Clostridium sp.})
    • Some conjugate (e.g., \textit{E. coli})
  – Plasmids
    • Small, circular, extrachromosomal DNA, are found mostly in Gram $\Theta$’s
    • Swapped during conjugation
  – Readily swap and incorporate DNA from other bacteria often via \textit{bacteriophages}, viruses that infect bacteria

\textit{Bacteria can not absorb folic acid, they must synthesize what they need to produce thymidine and uridine (nucleosides)}
Bacteria are Prokaryotes

• Metabolism
  – No membrane bound organelles
  – Cytoplasmic membrane executes functions of eukaryotic organelles
    • Energy production
    • Metabolic enzymes

• Other structures
  – Gram −’s have an outer membrane plus the inner cell membrane
  • In Gram −’s, the 
    periplasmic space
    (between the inner & outer cell membranes) contains hydrolytic enzymes, including collagenases, hyaluronidases, proteases, and β-lactamases.
Bacteria Basics

• Other structures
  – Some have a thick cell wall, some thin (or none)
  – Some have a lot of flagella, some have no flagella
  – Some have pili
  – Some have exterior polysaccharide capsule
    • Protection from phagocytes
    • Gram $\Theta$ lipopolysaccharides
      – Endotoxin

Endotoxic shock = septic shock

Mycoplasm don’t have a cell wall, and so are immune to $\beta$ lactam antibiotics!
$\beta$ Lactams include the penicillins...

Don’t confuse Mycoplasma (which may cause pneumonia) with Mycobacterium (which may cause TB)
Antibiotic Spectrum

Mycobacteria are “acid fast”

Some are **Bacteriocidal** (aminoglycosides, rifampin, quinolones), the rest are **Bacteriostatic**
Bacterial Basics

- The Gram stain sorts bacteria into 2 big groups
- Most antibiotics have effects against one or the other
  - Gram $\oplus$
    - Crystal violet or methylene blue: Stain *purple-blue*
    - Antibiotics with Gram $\oplus$ bacterial effects: Most $\beta$-lactams (cephalosporins, macrolides, penicillins), glycopeptides (Vancomycin, Teicoplanin), nitrofurantoin, polypeptides.
  - Gram $\ominus$
    - Basic fuchsine or safranin (basic red): Stain *pink*
    - Antibiotics with effects on Gram $\ominus$ bacteria: aminoglycosides
  - **Broad spectrum antibiotics:**
    - Ansamycins (mostly Gram $\oplus$), carbapenems, later generation cephalosporins, monobactams, quinolones, sulfonamides, tetracyclines

*Mycobacteria (e.g, TB) are neither Gram $\oplus$ or Gram $\ominus$*
Bacterial Basics

• Gram ⊕
  – Purple
  – More respiratory tract & skin pathogens
    • *Staphylococcus* sp.
    • *Streptococcus* sp.

• Gram ⊖
  – Stain pink (red)
  – Greater variety of pathogens (lots of GI)
    • *Neisseeia* sp. (gonorrhea)
    • *Salmonella* sp.
    • *Enterobacter* sp.
    • *Escherichia* sp.

Fun Facts

The GIT contains 1-2 kg of bacteria mainly species of:

*Bacteroides*, *Clostridium*,
*Fusobacterium*, and
*Peptostreptococcus*.

*Escherichia* sp. represent only a very small fraction of the ~500 species.

Gut microbes produce
Vitamins K & various B’s
Bacteria Basics

Gram ⓞ pathogens

• Cocci
  – Streptococcus sp.
  – Staphylococcus sp.

• Bacilli
  – Non spore forming
    • Corynebacterium sp.
    • Listeria sp.
  – Spore forming
    • Bacillus sp.
    • Clostridium sp.
Bacteria Basics

Gram negative pathogens

• Cocci (spheres)
  – *Neisseria gonorrhoeae*

• Bacilli (rods)
  – *Hemophilus influenzae*
  – *Escherichia coli*
  – *Helicobacter pylori*
Bacteria Basics

5 fundamental sites of action for antibiotics

- **Cell Wall Synthesis**
  - Penicillins, cephalosporins, glycopeptides, monobactams, Carbapenems, isoniazid

- **Protein Synthesis**
  - Aminoglycosides, Macrolides, Ketolides, Tetracyclines, Chloramphenicol, Oxazolidinones, Streptogramins, Rifampin

- **Modifies a membrane**
  - Paracelsin, Calcimycin, Gramicidin

- **Interrupts DNA Synthesis**
  - Fluoroquinolones, Nalidixic acid

- **Interferes with an enzyme**
  - Sulfonamides, Trimethoprim, Dapsone
Bacteria Basics

3 basic mechanisms of Plasmid-based resistance

1. Efflux pump superfamilies
   - Major facilitator superfamily (MFS)
   - ATP-binding cassette (ABC)
   - Small multidrug resistance (SMR)
   - Resistance-nodulation-cell division (RND)
   - Multi-antimicrobial extrusion protein family (MATE).

2. Antibiotic altering enzymes

3. Antibiotic degrading enzymes

Genes for ESBL (extended spectrum beta lactamases) are often coded for on Plasmids

www.textbookofbacteriology.net/ResistanceMechanisms.html
**UTIs are bacterial infections**

- ~10M Doctor visits/year
  - 2nd only to respiratory tract infections
  - 30:1 women:men
    - ♀ - shorter urethra, more prone to infection
    - ♂ - prostate issues after age 40
  - Patients with indwelling catheters
    - Often asymptomatic & not treated due to superinfection risk
  - The normal periurethral flora

*In infants <1 yr, 4:1 male:female*

*In ♀ >65 → 38% in community living, 27% in residential care & 55% in long-term care have asymptomatic bacteriuria*
Risk Factors for UTI

1. Abnormality or blockage
2. Catheters placed in bladder
   - Indwelling (Foley)
   - Intermittent (straight or coude tip)
   - Suprapubic
   - External (e.g., “condom” catheters)
3. Diabetes mellitus
4. Immunosuppression
5. Sexual intercourse (for women)
6. Diaphragm or spermicide use (in women)
7. Neurogenic bladder or bladder diverticulum
8. Postmenopausal women with bladder or uterine prolapse
9. Pregnancy (for women)
Getting UTIs

• Colonization
  – Entry by *ascent from urethra*
  – Rarely, by renal abscess or other route
  – Therefore *almost always fecal bacteria - E. coli*

• Host factors
  – Volume of urine
  – Epithelial cell sloughing (bacterial receptors on those cells)
  – Ureterovesical valves (where ureter enters bladder)
  – Ureter peristalsis

• Bacterial factors
  – Pili production (allows attachment)
  – Polysaccharide elaboration (protects from phagocytosis)
  – Hemolysin and endotoxin release (cause inflammation)
UTI Therapeutics

• Main cause, fecal bacteria:
  – *Escherichia coli* - up to 72%

• Others
  – *Staphylococcus saprophyticus* - up to 20%
  – *Klebsiella sp.* - up to 12%
  – *Enterococcus sp.* - up to 12%

• Two directions for therapy
  – Antibiotics
  – Drugs to acidify the urine
# UTI Treatment in Adults

Adapted from: N.R. Chamberlain, Ph.D., Associate Professor Microbiology and Immunology, Kirksville College of Osteopathic Medicine, A.T. Still University of Health Science. 04/07/08

<table>
<thead>
<tr>
<th>UTI Category</th>
<th>Principal pathogens</th>
<th>First-line therapy</th>
</tr>
</thead>
</table>
| Acute uncomplicated cystitis | *E. Coli*  
*Staphylococcus saprophyticus*  
*Proteus mirabilis*  
*Klebsiella pneumoniae* | Trimethoprim-sulfamethoxazole or TMP-SMX (Bactrim, Septra) 🎧ickt C  
Nitrofurantoin (Macrobid) 🎧ickt B  
Quinolones e.g., Ciprofloxacin (Cipro) 🎧ickt C |
| Complicated UTI           | *E. Coli*  
*K. pneumoniae*  
*P. Mirabilis*  
*Enterococcus sp.*  
*Pseudomonas aeruginosa* | Gram ⊗ - PO Quinolones (eg., Cipro, or Ofloxacin)  
Gram ⊕ - PO amoxicillin 🎧ickt B |
| Asymptomatic bacteriuria in pregnancy | Same as acute uncomplicated cystitis | Amoxicillin 🎧ickt  
Nitrofurantoin (Macrobid) 🎧ickt B  
Cephalexin (Keflex) 🎧ickt B  
NO TETRACYCLINES OR QUINOLONES |
| Catheter-associated UTI   | Depends upon the duration of catheterization | Gram ⊗ - PO Quinolone (e.g., Cipro) 🎧ickt  
Gram ⊕ - PO amoxicillin or amoxicillin + gentamicin (an aminoglycoside) 🎧ickt |
### Sulfonamide Antibiotics

**Antibiotics that interfere with metabolism**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadiazine</td>
<td>Broad spectrum of infections</td>
</tr>
<tr>
<td>Sulfisoxazole (Gantrisin)</td>
<td>Broad spectrum of infections including STDs</td>
</tr>
<tr>
<td>Sulfamethoxazole and trimethoprim (Septra) AKA: SXT, TMP-SMX… Co-trimoxazole (Bactrim)</td>
<td>Otitis media, bronchitis, UTI, shigellosis, fungal pneumonia caused by <em>Pneumocystis carinii</em> (<em>P. jiroveci</em>), and traveller’s diarrhea. Also, off label for Toxoplasmosis in HIV patients, #54 &amp; 62 generic by units sold in 2007 $\tau_{1/2} \approx 10$ hr</td>
</tr>
</tbody>
</table>

75% of kids experience acute otitis media before age 3. *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella* account for about 85% of cases of acute otitis media. Viruses account for the remaining 15%.

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**TMP-SMX mechanism**

ADRs:

- **Allergy** ~30%, including Stevens Johnson syndrome
- **Anemia** - *The risk of blood dyscrasias* is greater in patients with low folate levels: the elderly, alcoholics, malnourished...

For UTIs: PO BID (10-14 days). Also as IV infusion, but is too alkaline for parenteral use.

**Diagram:**

- Dihydropteroate diphosphate + p-aminobenzoic acid (PABA)
- Sulfonamides
- Dihydropteroate synthetase
- Trimethoprim
- Dihydrofolate reductase
- Tetrahydrofolate acid
- Thymidine
- Uridine

**G6PD**
TMP-SMX

• Kinetic/dynamic considerations
  – Okay PO absorption, liver metabolism, kidney excretion

• Contraindications and warnings
  – Allergy to sulfonamides, sulfonylureas, thiazide diuretics
  – Porphyria (= Heme problems; may trigger acute attack)
  – Pregnancy (may be teratogenic)
  – Lactation
  – Kidney disease or stones
    • Acute renal failure possible
  – May cause immunosuppression
  – Mydriasis
  – Hepatitis

Bacteriostatic

Resistance is common

G6PD

A. Beale

PHRM 203 - Micro 3
TMP-SMX

• ADRs
  – Allergic reactions
    • Common: rash, hives
    • Rare: SJS, TENs, agranulocytosis, hemolytic anemia, drug-induced immuno-thrombocytopenia (like heparin)
  – Drug reactions
    • +thiazide diuretics → thrombocytopenia & purpura
    • + warfarin →↑ prothrombin time
    • Bactrim →↑ levels of digoxin, sulfamethoxazole (when bactrim is given with indomethacin), methotrexate (PPB displacement), phenytoin
    • Efficacy of Tricyclic antidepressants is ↓
    • + Dofetilide (a class III antiarrhythmic)→↑ risk of arrhythmias

SJS = Steven Johnson Syndrome
TENs = Toxic Epidermal Necrosis

A. Beale
Nitrofurantoin (MacroBid) 🌞 B

- **Take WITH food (NOT w/Mg++)**
  - ↑ absorption 45%
  - Probenecid ↑ serum levels
- **Indication:** UTIs
- **ADRs include**
  - GI upset, hypersensitivity pneumonitis and *if used chronically can cause pulmonary interstitial fibrosis and peripheral neuropathy*
  - Cholestatic jaundice/hepatic dysfunction
    - Dark orange-brown urine
  - Peripheral neuropathy (may be severe & permanent)
  - **Contraindicated in:**
    - Babies <1 month old or late in pregnancy (lack metabolism)
    - Glucose-6-phosphate dehydrogenase deficient people
    - Kidney disease, anuria (no urine) or oliguria (reduced urine output)
    - May cause false + Urine glucose test (Benedict’s or Fehling’s)
Nitrofurantoin sites of action

Nitrofurantoin metabolized to reactive species with many effects

Nitrofurantoin damages the nucleoid DNA

Resistance is NOT an issue!

Nitrofurantoin reacts with RNA

Nitrofurantoin interferes with cell wall synthesis

Nitrofurantoin interferes with Bacterial CBH metabolism

Resistance is NOT an issue!
## Fluoroquinolones (Quinolones)

⊗ DNA replication; Generally, very Broad Spectrum

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADRs</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (Cipro, Proquin)</td>
<td>Fluoroquinolones HAVE LOTS OF BAD ADRS!!!</td>
<td>Gram + &amp; - infections including <em>Salmonella enterica</em> Serovar <em>typhi</em> (Typhoid fever, G-), anthrax G +, methacillin susceptible bacteria &amp; UTIs. IV t ½ 5-6 hr; PO t ½ ~ 4 hr. Also available as eye/ear drops.</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Serious CNS effects</td>
<td>UTI, anthrax, etc.</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Serious CV effects</td>
<td>Chronic bronchitis, etc</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Tendon rupture</td>
<td>UTIs</td>
</tr>
<tr>
<td>Ophthalmic only</td>
<td>Peripheral neuropathy</td>
<td>Lung, skin, eyes, UTIs</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Metabolic effects….</td>
<td></td>
</tr>
</tbody>
</table>
Fluoroquinolone site of action

**Resistance is common**

**Bactericidal**

**Fluoroquinolones target the nucleoid DNA**

**Gram -** target = DNA Gyrase

**Gram +** target = Type IV topoisomerase

Fluoroquinolones easily enter cells (ours & bacterial) via porin

Gyrase - Supercoils DNA
Topoisomerase - reconnects broken strands
Fluoroquinolones: Cipro

• Kinetic/dynamic considerations
  – Well absorbed PO *(Don’t take with food!)*
    • NOT WITH multivalent cations
      – Ca++, Fe++, Mg++, Zn++, Al++, e.g., multivitamins, antacids)
    • ↓ bioavailability up to 90%

• Contraindications/warnings
  – Allergy
  – Co-administration with tizanidine (CNS α2 agonist) - potentially fatal hypotension & sedation
  – Use with caution in patients with seizure history (NSAIDS risk)
  – Don’t take with theophylline, caffeine, sucralfate, didanosine
  – Warfarin effects ↑ (PT ↑)

Ciprofloxacin  ≠  Cephalexin

Θ P450s

Potentially fatal
Fluoroquinolones

• ADRs - warnings upgraded regularly
  – CNS & PNS
    • Headache, dizziness, insomnia, increased intracranial pressure, fever, tinnitus, depression, anxiety, fear, blurred vision, nightmares, confusion, psychosis, twitching, tingling, numbness, muscle weakness, seizures

  – Cardiac
    • Tachycardia, palpitations

Fluoroquinolones have the highest risk of MRSA &/or CDAD of any antibiotic class

Cipro blocks the P450 metabolism of caffeine & theophylline causing:
  • Hyperexcitability, seizures, status epilepticus, cardiac arrest, respiratory failure
Fluoroquinolones

• ADRs - Continued
  – GI, Liver & Kidney
    • Hepatitis → jaundice, necrosis or liver failure
    • Interstitial nephritis → acute renal insufficiency or failure
    • Nausea, vomiting, diarrhea, dry mouth, CDAD
  – Immune system
    • Anaphylaxis on FIRST dose
    • Bone marrow depression and multiple blood dyscrasias
    • Rash → SJS or toxic epidermal necrolysis (TENS)
  – Other
    • Photosensitivity, hair loss, cartilage damage and tendon rupture

**Boxed warning**

If used to treat UTI, encourage cranberry juice consumption to acidify urine.
## Urine Acidifiers

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methenamine (Hiprex)</td>
<td>GI upset; bladder irritation; X placenta &amp; into milk</td>
</tr>
<tr>
<td>Methylene blue (Urolene Blue)</td>
<td>Tissue staining &amp; GI upset; bladder irritation; X placenta &amp; into milk</td>
</tr>
</tbody>
</table>

### PO for UTI, slow IV for methemoglobinemia

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Some MAOI by Methylene Blue, so Serotonin Syndrome alert
UT Analgesia

![Phenazopyridine (Baridium)](https://example.com) B OTC

- Dye
- Local anesthetic effect on bladder mucosa
- Given in combo with antibiotic
  - NEVER ALONE!!
- Rapid PO absorption, hepatic metabolism, renal excretion (65% unchanged)
- ADRs
  - Allergy, GI upset, headache, discoloration of urine that stains clothing. Potential for hepatic/renal toxicity

PO TID (not for >2days)
Bladder protectants

🎉 Pentosan Polysulfate Sodium (Elmiron)

– Adheres to bladder wall and affords protection from irritant action of other drugs

– Heparin-like
  • Anticoagulant & fibrinolytic
  • May induce thromobocytopenia

– Poorly absorbed (3%) PO - dose: 100 mg PO tid

PO 1 hour before or 2 hours after meals
Antispasmodics

- Innervation of bladder
  - Ureters
    - PSNS (peristalsis to move urine from kidneys to bladder)
  - Detrusor muscle
    - SNS (relaxation – allows filling)
    - PSNS (contraction – voids urine)
  - Internal sphincter
    - PSNS (relaxation)
    - SNS (contraction)
  - External sphincter
    - Somatic (voluntary control – contraction, until bladder “full” then involuntary relaxation)

## Antispasmodics
Muscarinic antagonists for overactive bladder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin (Enablex)</td>
<td>ACh M₃ blocker</td>
<td>CYP inhibitors</td>
</tr>
<tr>
<td>Flavoxate (Urispas)</td>
<td>Anti-ACh</td>
<td>GI upset, confusion</td>
</tr>
<tr>
<td>Oxybutynin (Ditropan)</td>
<td>Anti-ACh M₁₋₃</td>
<td>antipsychotics</td>
</tr>
<tr>
<td>Solifenacin (VESIcare)</td>
<td>Anti-ACh M₁₋₃</td>
<td>CYP inhibitors, dry mouth, constipation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>headache, confusion, dry eyes.</td>
</tr>
<tr>
<td>Tolterodine (Detrol)</td>
<td>Anti-ACh M₁₋₂</td>
<td></td>
</tr>
<tr>
<td>Trospium (Sanctura)</td>
<td>Anti-ACh M₁₋₃</td>
<td></td>
</tr>
</tbody>
</table>

PO SID, take with water, do not crush

Avoid using anticholinergics in glaucoma patients

Avoid using anticholinergics in glaucoma patients
Benign Prostatic Hyperplasia

• α1 blockers
  – Doxazosin (Cardura)
    • BPH & HT
  – Tamsulosin (Flomax)
    • BPH only
  – ADRs
    • 1st dose syncope
    • Hypotension
    • Priapism
  – Others include alfuzosin (Uroxatral) and terazosin (Hytrin)

• Anti-androgen
  – Finasteride (Proscar, Propecia)
    • Θ 5-α-reductase, so ⊗ testosterone → dihydroxytestosterone (DHT stimulates the prostate)
    • May cause impotence
    • Should not be handled by pregnant women
    • Takes months before effects seen, a year to reverse
    • Another is dutasteride (Avodart)

PO SID
titrate 1-2 weeks between changes in dosage
# Acne

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications/ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin (Accutane, Sotret) 🏥 ⚫ X</td>
<td>PO (20 weeks) Retinoid for <strong>severe recalcitrant nodular acne</strong>. Must be taken with fatty food. Used off label (PO for 6 months) to reduce the regrowth of neuroblastoma in kids after high dose chemo and skin cell therapy (transplant).</td>
</tr>
<tr>
<td>Adapalene (Differin) 🏥</td>
<td>Topical for <strong>acne vulgaris</strong>. Up to 40% experience skin redness, dryness, scaling. Topicals not associated with birth defects.</td>
</tr>
<tr>
<td>Doxycyline (Vibramycin)</td>
<td>See Micro 2, many indications including PO for <strong>severe acne</strong>. Superinfection risk.</td>
</tr>
<tr>
<td>Benzyl peroxide + clindamycin (BenzaClin)</td>
<td>Topical for <strong>acne vulgaris</strong>. Clindamycin is absorbed through the skin and can cause GI superinfections.</td>
</tr>
</tbody>
</table>
Isotretinoin (Accutane, Sotret)

- Known teratogen
- High risk during 1st trimester (even in small amounts):
  - Hydrocephaly
  - Microcephaly
  - Mental retardation
  - Ear/eye abnormalities
  - Cleft palate
  - Other facial deformities
  - Heart defects
  - Risk of premature birth and fetal death

Other ADRs:
- Similar to Vitamin A toxicity
  - Dry, cracked lips, skin and mucous membranes
  - Benign intracranial hypertension
  - Psychiatric events

Interactions
- iPLEDGE Program requires birth control, but Isotretinoin may interfere with oral contraceptives

Other PO retinoids
- Soritane (acitretin) for psoriasis
- Vesanoid (tretinoin) for acute promyelocytic leukemia
- Targretin (bexarotene) for T-cell lymphoma

Boxed warning: Only distributed under iPLEDGE program.