A BRIEF HISTORY OF ANTIBIOTICS – THE DISCOVERY OF PENICILLIN

- 1928 - Penicillin accidentally discovered by Alexander Fleming
- 1941 - Isolated at Oxford and administered to a patient
- 1945 – Enough drug produced in preparation for D-Day
- 1945 – Fleming, Chain, Florey awarded Nobel Prize
  - “It is not difficult to make microbes resistant to penicillin”
A BRIEF HISTORY OF ANTIBIOTICS

WHY SO MUCH INTEREST IN ANTIBIOTICS?

Antibiotics are a limited resource! Antibiotic resistance is a world health issue!
ANTIBIOTICS ARE HARD!

Drug

PK and Toxicity

PD and susceptibility

Patient

Organism

Infection and Immune Response

• PK is what the body does to the drug
• PD is what the drug does to the organism and body

OVERVIEW

• Antibiotic mechanisms of action

• Antibiotic Resistance

• How to select an antibiotic

• Common infectious disease treatments

• Antibiotic monitoring and common adverse reactions
HOW DO ANTIBIOTICS WORK?

Protein Synthesis Inhibitors Acting on Ribosomes
- Site of action: 50S subunit
  - Erythromycin
  - Clindamycin
  - Vancomycin
  - Linezolid

- Site of action: 30S subunit
  - Aminoglycosides
  - Gentamicin
  - Tobramycin
  - Tetracyclines
  - Chloramphenicol

- Both 30S and 50S
  - Inhibits initiation of protein synthesis
  - Unicodin

Cell Wall Inhibitors
- Cell membrane
  - Cause loss of selective permeability
    - Polymyxin
    - Daptomycin

- Inhibit replication and transcription
  - Nalidixic acid (unwinding enzyme)
  - Quinolones
  - Inhibit DNA polymerase
  - Mitomycin

Folic Acid Synthesis in the Cytoplasm
- Block pathways and inhibit metabolism
  - Sulfonamides (sulfon drug)
  - Trimethoprim

Different Classes of Antibiotics - An Overview

5-LACTAMS
- Commonly act as bacteriocidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

AMINOGLYCOSIDES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

GLYCOPROTEIN
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

STREPTOMYCN
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

SULFONAMIDES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

TETRACYCLINES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

MACRUBIUMS
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

OXAZOLIDINONES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

QUINOLINES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death

LIPOPOLYSACCHARIDES
- Commonly act as bacteroidal agents, restricting growth & reproduction
- Commonly act as bacteroidal agents, causing bacterial cell death
PENICILLINS – NARROW SPECTRUM

- Gram-positive activity
  - Natural: Penicillin (PCN) IV (PenG) or PO (PenVK)
    - Spectrum: Streptococcus, gram-positive anaerobes
    - Use: Dental prophylaxis, syphilis
  - PCNase-resistant: Nafcillin (IV), Oxacillin (IV), Dicloxacillin (PO)
    - Spectrum: Methicillin-Sensitive Staph. Aureus (MSSA)
    - Use: Endocarditis, Cellulitis (caused by above)
  - Aminopenicillins: Ampicillin (IV), Amoxicillin (PO)
    - Spectrum: Streptococcus, Enterococcus sp., Listeria
    - Use: Pneumonia, Upper Respiratory Tract Infections (URTI), Urinary Tract Infections (UTI)

PENICILLINS – BROAD SPECTRUM

- Gram-positive, gram-negative, anaerobes
  - Extended Spectrum PCN: Piperacillin, Ticarcillin (IV)
    - Spectrum: Gram-negative organisms, Pseudomonas
    - Use: Rarely used without beta-lactamase inhibitors
  - Amp/sulbactam (Unasyn IV) or Amox/clavulanic acid (Augmentin PO)
    - Spectrum: Streptococcus, Enterococcus sp., anaerobes, gram-negatives
    - Use: Pneumonia, URTIs, UTIs, Intra-abdominal infections
  - Pip/tazobactam (Zosyn IV), Ticar/clavulanate (Timentin IV)
    - Spectrum: Sensitive gram-positive, Better gram-negative, Pseudomonas, anaerobes
    - Use: All types of infections, empiric coverage
CEPHALOSPORINS

1<sup>st</sup> Generation | 2<sup>nd</sup> Generation | 3<sup>rd</sup> Generation | 4<sup>th</sup> Generation
--- | --- | --- | ---
Anaerobes | MSSA Coverage | *Not Ceftazidime | NO ENTEROCOCCUS or MRSA COVERAGE... yet
Streptococcus | Gram Negative Coverage

Outpatient use: dental prophylaxis, syphilis
Inpatient and outpatient use: endocarditis, cellulitis
Inpatient use: pneumonia, intraabdominal
Inpatient and outpatient use: most infections
CEPHALOSPORINS

• 1st: Cephalexin (PO), Cefazolin (IM, IV)
  • Spectrum: MSSA, “PEK” organisms (Proteus, E. coli, Klebsiella)
  • Use: Pneumonia (outpatient), Cellulitis, UTIs

• 2nd: Cefoxitin (IV), Cefaclor (PO)
  • Spectrum: MSSA, Streptococcus, anaerobes, “HeNPEK” (Haemophilus, Neisseria, Proteus, E. coli, Klebsiella)
  • Use: GI surgical prophylaxis

• 3rd: Ceftriaxone (IV, IM) Cefixime (PO)
  • Spectrum: Streptococcus, “HeNPEK M” (Haemophilus, Neisseria, Proteus, E. coli, Klebsiella and Moraxella)
  • Use: Meningitis, pneumonia (hospitalized patients)

• 3+: Ceftazidime (IV)
  • Spectrum: Pseudomonas, “HeNPEK M”, no gram positive

• 4th: Cefepime (IV)
  • Spectrum: Pseudomonas, best gram-negative of cephalosporins, sensitive gram-positive
  • Use: All types of infections, empiric coverage

• 4+: Ceftaroline:
  • Spectrum: Staphylococcus aureus (MRSA/MSSA), Streptococcus, H.influenzae, Klebsiella, E.coli
  • Use: Skin and soft tissue infections, Community-acquire pneumonia

CARBAPENEMS – DRUGS OF LAST RESORT (OFTEN)

• Meropenem, Imipenem, Doripenem (IV)
  • Spectrum: MSSA, Streptococcus, Pseudomonas, Acinetobacter, Great Gram-negative coverage even ESBL and Ampc producing “superbugs”, anaerobes
  • Use: One of the last line of defense for highly resistant organisms – use cautiously

• Ertapenem (IV)
  • Spectrum: MSSA, Streptococcus, Anaerobes, Gram-negatives not Pseudomonas or Acinetobacter
  • Use: One time dose for surgical prophylaxis
IMPACT OF BETA-LACTAM ALLERGIES

• Outpatient clinic
  • 99/660 patients had documented beta-lactam allergy
    • Only 33 (33%) had a description of allergy
    • Mean antibiotic costs: $26.61 in allergy patients; $16.28 in non-allergy patients
    • Allergy patients more likely to receive cephalosporin, macrolide or miscellaneous antibiotic

• Inpatient
  • 118 penicillin allergic patients and 118 non-allergic matched controls
    • 33% of penicillin allergy patients could describe reaction
    • Mean antibiotic costs: $81.70/day in allergy patients vs. $52.50/day in non-allergy patients
    • Allergy patients more likely to receive cephalosporin, vancomycin, or miscellaneous antibiotic

• Penicillin allergies are linked to increases in C. difficile, MRSA, and VRE infections
  • 2013 retrospective, matched cohort study
    • Significantly more fluoroquinolone, clindamycin, and vancomycin use (p<0.0001)
    • 23.4% more C. difficile (95% CI: 15.6%-31.7%)
    • 14.1% more MRSA (95% CI: 7.1%-21.6%)
    • 30.1% more VRE infections (95% CI: 12.5%-50.4%)


HOW CAN YOU HELP YOUR RESIDENTS?

• When did it happen?
  • Age at the time of the reaction
  • Time of onset of the reaction after beginning the medication
  • Indication for medication – concurrent medications? Concurrent viral infection?
  • Family history of allergy is not significant!

• What happened?
  • Signs/symptoms of the reaction
    • Antidote given? visit to emergency room? loss of consciousness? difficulty breathing?
    • Did you seek medical treatment?

• Have you received similar medications since that reaction?
  • Route of administration (oral or IV)
    • Anaphylactic reactions to oral medications are less frequent
    • If yes, what was the outcome?

• Did the reaction abate after the medication was discontinued?
WHAT RASH IS IT?

- Urticaria (IgE-mediated) rashes are an intensely pruritic, circumscribed, raised and erythematous eruption with central pallor.
  - Usually occur within minutes to hours of receiving offending agent, but may occur up to 72 hours after administering.\(^{31}\)

- Macular papular or morbilliform rashes (non-IgE-mediated) begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.
  - Usually occur > 72 hours after receiving offending agent.

URTICARIAL RASH – IGE-MEDIATED

intensely pruritic, circumscribed, raised and erythematous eruption with central pallor

MACULAR PAPULAR OR MORBILLIFORM RASHES – NON-IGE MEDIATED

Begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.

Avoid antibiotic of same/similar class if patient reports:

- IgE-mediated reaction within 24 hours of receiving
  - Immediate urticarial rash
  - Angioedema
  - Anaphylaxis
- Severe, non-IgEmediate reaction
  - Stevens Johnson Syndrome
  - Toxic Epidermal Necrolysis
- Treatment choices
  - First line: use non-β-lactam antibiotic
  - Second line: PCN/cephalosporin/carbapenem desensitization under guidance of Allergist
  - Aztreonam use notes
    - Do NOT use if ceftazidime allergic
    - ONLY provides Gram negative coverage, no Gram positive activity
GIVE ANTIBIOTIC OF SAME CLASS IF...

• Patient has received in the past AFTER the reported reaction
  • Example: Patient reports GI upset with Augmentin but has received and tolerated ampicillin/sulbactam

• Patient reports a known side effect
  • Example: nausea and vomiting

GIVE ANTIBIOTICS OF SIMILAR CLASS IF...

• Similar class NO graded challenge
  • Reaction is ‘unknown’
  • Reaction is non-severe
  • Reaction is non-IgE mediated occurring AFTER 72 hours

• Similar class via GRADED CHALLENGE
  • Reaction is possible IgE-mediated occurring between 24 and 72 hours
    • Example: rash +/- hives
CROSS REACTIVITY BETWEEN PCN AND CEPHALOSPORINS

- < 1980: reaction rates reported 10-20%<sup>3</sup>
  - Cephalothin and cephaloridine share side chain with penicillin
  - Contamination prior to GMP
  - Confounding by inclusion of nonallergic ADRs<sup>2</sup>

- Advent of 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> generation cephs<sup>3</sup>
  - Do not share a side chain
  - Rate of rashes from cephalosporins = 1-3%

- Cross reactivity rate between PCN and cephs <1% if using 2<sup>nd</sup> or 3<sup>rd</sup> gen ceph<sup>4</sup>

4. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2002;89(2) 259-273

CROSS REACTIVITY WITH CARBAPENEMS

- Variable and studies are poor quality

- Reported cross reactivity rate of 9-11%
  - Retrospective
  - No PCN allergy verification
  - PCN ‘allergies’ could be ADRs and non-IgE mediated reactions

- Currently available carbapenems do NOT share a side chain with any PCN or cephalosporin

### SIDE CHAINS

**Chemical structure of penicillin**

![Chemical structure of penicillin](image1)

**Chemical structure of cephalosporin**

![Chemical structure of cephalosporin](image2)

**Chemical structure of carbapenem**

![Chemical structure of carbapenem](image3)

**Chemical structure of aztreonam**

![Chemical structure of aztreonam](image4)


### FDA-APPROVED BETA-LACTAM ANTIBIOTICS WITH SIMILAR SIDE CHAINS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agents with Similar Side Chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cefaclor</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Cefaclor</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Cephalasin</td>
<td>Cefditoren</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Cefditoren</td>
</tr>
</tbody>
</table>

*Agents not listed are either not approved for use in the United States (ceftizoxime, ceftibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin)

*Aztreonam only cross-reacts with ceftazidime, with which it shares an identical side-chain

*Identical R1 side chain

*Identical R2 side chain
**DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW**

**FLUOROQUINOLONES**

- Ciprofloxacin, Levofloxacin, Moxifloxacin

- MOA: Inhibit DNA gyrase and topoisomerase, enzymes required for replication
**FLUOROQUINOLONES**

**“Respiratory Quinolones”**

<table>
<thead>
<tr>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pseudomonas</strong></td>
<td>Anaerobes</td>
<td></td>
</tr>
<tr>
<td>Gram-negatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus</strong></td>
<td></td>
<td>MSSA</td>
</tr>
<tr>
<td><strong>MSSA</strong></td>
<td></td>
<td>Atypicals</td>
</tr>
</tbody>
</table>

**NO ENTEROCOCCUS or MRSA COVERAGE**

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**Ciprofloxacin (IV or PO)**
- Spectrum: Gram-negatives, Pseudomonas, No Gram-positive, No Anaerobic
- Use: Pneumonia when Pseudomonas is suspected, UTIs

**Levofloxacin (IV or PO)**
- Spectrum: MSSA and Strep. (not as potent as Moxifloxacin) and Gram-negative including Pseudomonas (not as potent as Ciprofloxacin), No Anaerobic, Atypicals
- Use: URTIs, Pneumonia

**Moxifloxacin (IV or PO)**
- Spectrum: MSSA and Strep., Anaerobes, Atypicals and Gram-negatives but NOT Pseudomonas
- Use: URTIs, Pneumonia when Pseudomonas is not suspected
FLUOROQUINOLONE ADVERSE REACTIONS

- QT prolongation \( \rightarrow \) Cardiac Arrhythmias
- Tendon rupture (especially children and beagles)
  - Not FDA approved for children < 18 years old
- Sun-sensitivity
- Central Nervous System (CNS) side effects
- Super-infections
  - *Clostridium difficile*
  - Resistant gram-negatives
  - MRSA
- Many drug interactions
  - Antacids or supplements containing Calcium, Iron, Magnesium, Aluminum can decrease oral absorption
  - Warfarin and Theophylline

FLUOROQUINOLONE FDA WARNING!

- Serious side effects associated with FQ outweigh the benefits of FQ use
- Fluoroquinolones are the drugs of last resort for acute sinusitis, acute bronchitis, and UTI
- Reserve FQ use for patients who do not have alternative treatment options
AMINOGLYCOSIDES

• Gentamicin, Tobramycin, Amikacin, Streptomycin

• MOA: Inhibit 30S subunit of the ribosome, ultimately inhibiting protein synthesis

AMINOGLYCOSIDES

• Intravenous therapy

• Use fell out of favor due to side effects
  • Kidney toxicity (tubular obstruction and renal vasoconstriction)
  • Ear toxicity (oto- and vestibular toxicity)

• Increased use due to antibiotic resistance

• Keep courses short (if possible) and use optimal dosing (once daily, high dose)
HOW DO ANTIBIOTICS WORK? – GRAM POSITIVES!

GLYCOPEPTIDES - VANCOMYCIN

- Vancomycin (IV and PO)
  - PO for *Clostridium difficile* only!
- MOA: Inhibit cell wall synthesis

  - Pros
    - Old drug, well studied
    - Multiple daily doses
    - Active against most Gram-positive organisms
    - Inexpensive
  - Cons
    - Only IV available
    - Acute kidney injury
    - “Narrow” therapeutic index
    - Monitoring needed
LIPOPEPTIDES - DAPTOMYCIN

- Daptomycin (IV)
- MOA: Disrupt cell wall integrity and allows escape of intracellular components
  - Pros
    - Once daily dosing
    - Active against most Gram-positive organisms
    - Relatively safe
    - No serum drug concentration monitoring
  - Cons
    - Expensive
    - Only IV available
    - Muscle toxicity

OXAZOLIDINONES - LINEZOLID

- Linezolid (IV and PO), Tedizolid (PO)
- MOA: Inhibit protein synthesis
  - Pros
    - Oral drug with good bioavailability
    - Active against most Gram-positive organisms
    - No serum drug concentration monitoring
  - Cons
    - Leukopenias with long-term therapy
    - Appropriate for severe disease?
    - Expensive – sort of.
LIPOGLYCOPEPTIDES – TELAVANCIN, ORITAVANCIN, DALBAVANCIN

• Two mechanisms of action!
  • Transglycosidation and transpeptidation

• Pros
  • Once weekly dosing possible (orita and dalba)
  • Low risk for resistance development
  • Well tolerated

• Cons
  • EXPENSIVE!!!
  • New agents, not extensively studied
  • Use outside of acute bacterial skin and skin structure infections is limited

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW
SULFONAMIDES – TMP/SMX OR BACTRIM

- Trimethoprim/sulfamethoxazole (IV and PO)
- MOA: Prevent important bacterial metabolic pathway
  - Pros
    - Old drug, well studied
    - Oral drug with good bioavailability
    - Active against broad spectrum of bacteria
    - No serum drug concentration monitoring
  - Cons
    - Inexpensive
    - Increasing rates of resistance, especially in urine
    - Rash is common
    - Photosensitivity and anemia

MACROLIDES – AZITHROMYCIN, ERYTHROMYCIN, CLARITHROMYCIN

- Azithromycin (IV and PO), erythromycin (PO), clarithromycin (IV and PO)
- MOA: Inhibit protein synthesis
  - Pros
    - Oral drugs with good bioavailability
    - Active against broad spectrum of bacteria
    - No serum drug concentration monitoring
  - Cons
    - Inexpensive
    - Increasing rates of resistance
      - Erythromycin ineffective
    - Commonly cause GI upset
**URINE AGENTS!**

- **Nitrofurantoin**
  - Concentrates in the urine, avoids systemic exposure
  - Activity against MDR pathogens
  - Dose 100mg PO BID
  - Caution with severe renal dysfunction

- **Fosfomycin**
  - Concentrates in the urine, minimal systemic effect at oral doses
  - Activity against XDR pathogens
  - Dose 3gm PO x1 or q72 hours x3 doses

---

**DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW**

- **β-Lactams**
- **Aminoglycosides**
- **Chloramphenicol**
- **Glycopeptides**
- **Aminoglycosides**
- **β-Lactams**
- **Tetracyclines**
- **Macrolides**
- **Quinolones**
- **Lipopeptides**

**Key:**
- Commonly act as bacteriostatic agents, restricting growth & reproduction
- Commonly act as bactericidal agents, causing bacterial cell death

**Discovery:**
- 1830
- 1940
- 1960
- 1970
- 1980
OVERVIEW

• Antibiotic mechanisms of action

• Antibiotic resistance

• How to select an antibiotic

• Common infectious disease treatments

• Antibiotic monitoring and common adverse reactions

ANTIBIOTIC DEVELOPMENT

• Antibiotics are a limited resource!

- New Antibacterial Agents

- Increase in Antibiotic Resistance

• ADAPT Act, GAIN Act allow for access to novel drugs based on limited clinical trial information
EMERGING THREATS

**Urgent**
- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug-resistant *Neisseria gonorrhoeae*

**Serious**
- MDR *Acinetobacter, Pseudomonas, Salmonella, Shigella*, tuberculosis
- ESBLs
- MRSA
- Drug-resistant *Strep pneumoniae*

**Concerning**
- Vancomycin-resistant *Staphylococcus aureus*
- Erythromycin-resistant *Streptococcus Group A*
- Clindamycin-resistant *Streptococcus Group B*
**ANTIBIOTIC RESISTANCE IS REAL**

CDC calls on hospitals, doctors to fight antibiotic resistance

**NEW DRUGS, NEW RESISTANCE**

The rise of resistance

- Ceftaroline
- Daptomycin
- Linezolid
- Levofloxacin
- Ceftazidime
- Imipenem
- Vancocin
- Gentamicin
- Methicillin
- Erythromycin
- Tetracycline
- Penicillin

CAUSES OF ANTIBIOTIC RESISTANCE

CDC Core Elements of Antibiotic Stewardship in Nursing Homes

ANTIBIOTIC PRESCRIBING PATTERNS
ANTIMICROBIAL USE AND MISUSE

- Antibiotics are 2nd most commonly prescribed drug in the US
  - Approximately $10 billion dollars per year

- 50% of UWHC patients receive antibiotics

- 40-75% of nursing home residents receive unnecessary antibiotics

- 50% of ALL antibiotic use is inappropriate!


OVERVIEW

- Antibiotic mechanisms of action

- Antibiotic resistance

- How to select an antibiotic

- Common infectious disease treatments

- Antibiotic monitoring and common adverse reactions
HOW TO SELECT THE BEST ANTIBIOTIC

1. Is the patient infected?
2. What is the site of infection?
   • Non pharmacologic options possible (examples: necrotizing infections, abscess present, prosthetic hardware lower extremity cellulitis)
   • Difficult to penetrate site (prostate, eye, CSF, lungs, bone)
3. Social factors?
   • Infusion time or ability to get to specialized infusion center
4. What organism(s) are likely causing the infection?
   • Recent microbiologic culture results
   • History of colonization or previous infection
5. What antibiotics are potential options for this infection and what makes them different from one another?
   • Spectrum
   • Route of administration
   • Toxicities
   • Comorbidities (renal or liver drug clearance and renal or liver dysfunction)
6. What makes this patient unique?
   • Weight, age, sex, allergies

Efficacy = Safety > Social = Fiscal Responsibility

• Efficacy
  • Most likely to be active against likely pathogens
  • Cidal vs. Static

• Safety
  • Comorbidities
  • Allergies

• Social Responsibility
  • Effect of antibiotics on the rest of the population

https://www.idstewardship.com/insights-resources/antibiotic-renal-dose-adjustments/
OVERVIEW

• Antibiotic mechanisms of action

• Antibiotic resistance

• How to select an antibiotic

• Common infectious disease treatments

• Antibiotic monitoring and common adverse reactions

SKIN AND SOFT TISSUE INFECTION

• 86 year old LTAC resident complains of LE pain and swelling.
SSTI – IS THE PATIENT INFECTED?

• Myth 1: All red and swollen skin is cellulitis.
• Myth 2: Bilateral leg swelling and redness is cellulitis.

MYTH 1: ALL RED AND SWOLLEN SKIN IS CELLULITIS.

Common signs/symptoms
• Peripheral edema
• Erythema
• Warmth
• Tenderness
• “Orange peel” appearance
• Vesicles
• Bullae
• Petechiae
• Pain

MYTH 1: ALL RED AND SWOLLEN SKIN IS CELLULITIS.

Common signs/symptoms

- Peripheral Edema

Alternative Peripheral Edema Causes

- Heart failure
- Cirrhosis (hypoalbuminemia)
- Primary renal sodium retention
  - Nephrotic syndrome
  - NSAIDs, glitazones, hormone therapy, vasodilators, Ca²⁺ channel blockers
- Fluid overload (parenteral therapy?)
- Venous thrombosis or stenosis
- Chronic venous insufficiency (post thrombosis)
- Trauma (inflammation)
- Allergic reactions
- Drug reactions (gabapentin, pregabalin, pramipexole, ropinirole)


MYTH 1: ALL RED AND SWOLLEN SKIN IS CELLULITIS.

Common signs/symptoms

- Erythema

Non-infectious erythema Causes

- Pruritus
  - Drug induced?
  - Lymphoma
  - Iron deficiency
  - Thyroid abnormalities
- Eczema
- Trauma
- Contact dermatitis
- Chronic venous insufficiency
- Skin neoplasia

MYTH 2: BILATERAL LEG SWELLING AND REDNESS IS CELLULITIS.

- Bilateral leg cellulitis is exceedingly rare
  - LE cellulitis commonly caused by breach in skin barrier
  - Independent infection of both legs would be required for bilateral cellulitis

- Common causes of bilateral leg swelling include: chronic stasis dermatitis, deep vein thrombosis (DVT), heart failure, venous stasis, and lymphedema

- Role of the passive leg raise during diagnosis

PASSIVE LEG RAISE AND TREATMENT OF BILATERAL LE CELLULITIS

- Passive leg raise should alleviate erythema and swelling if non-infectious (promotes gravity drainage of edema and inflammatory substances)

- Treatment if non-infectious
  - Elevate affected area TID
  - Apply elastic bandages from toes to thighs q8hrs
SSTI – SITE OF INFECTION AND SOCIAL FACTORS

• What is the site of infection?
  • Size of the infection? I&D alone ok?
  • Abscess/Purulence present? More to come
  • Difficult to penetrate site? --- Not an issue with SSTI
  • Necrotizing infection? If yes, then needs surgery

• Social factors?
  • Ability to provide IV therapy?
  • Insurance coverage?
  • Ability to get to specialized infusion center?
  • Central line placement?

SSTI – POSSIBLE PATHOGENS

• What organism(s) are likely causing the infection?
  • Recent microbiologic culture results
  • History of colonization or previous infection
  • The majority of skin, skin structure, and soft tissue infections (60-90%) are caused by Gram-positive organisms.
    • *Staphylococcus ssp*
      • MRSA
      • MSSA

• *Streptococcus ssp*
  • Group A
  • other β-hemolytic streptococci
SSTI – POSSIBLE PATHOGENS

- Do I Need Gram Negative Coverage?
- Complicating factors that increase suspicion of Gram-negative (most likely E.coli) organisms
  - Infection while swimming
  - Infection near groin or rectum
  - Ulcers soaked in water
  - Diabetes mellitus
  - Vascular insufficiency
  - Periorbital cellulitis
  - Immunosuppression
  - Healthcare system contact within the past 90 days
- < 5% of chronic diabetic foot infections involve *Pseudomonas* spp
- Risk factors for infections caused by *Pseudomonas aeruginosa*
  - Nosocomial or healthcare-associated infection
  - Soaking of open wound in tap water

SSTI – POTENTIAL ANTIBIOTIC THERAPY

<table>
<thead>
<tr>
<th>Intravenous Therapy</th>
<th>Oral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus sp.</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Streptococcus sp. and MSSA</td>
<td>Oxacillin/Nafcin</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Streptococcus sp., MSSA and MRSA</td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
</tr>
<tr>
<td></td>
<td>Telavancin</td>
</tr>
<tr>
<td></td>
<td>Ceftaroline</td>
</tr>
<tr>
<td></td>
<td>Oritavancin/Dalbavancin</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole PLUS Streptococcus drug</td>
<td></td>
</tr>
<tr>
<td>Doxycycline OR minocycline PLUS <em>Streptococcus</em> drug</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
</tr>
</tbody>
</table>

What makes this patient unique?
Weight, Age, Sex, Allergies?
### GENERAL PRINCIPLES – SELECTING AN ANTIBIOTIC

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abscess</td>
<td>Cephalexin or Dicloxacillin</td>
<td>Cefazolin or Oxacillin</td>
</tr>
<tr>
<td>Abscess w/o</td>
<td>I&amp;D + TMP-SMX</td>
<td>I&amp;D + Vancomycin</td>
</tr>
<tr>
<td>surrounding cellulitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess w/</td>
<td>I&amp;D + TMP-SMX + Cephalexin</td>
<td>I&amp;D + Vancomycin + Cefazolin</td>
</tr>
<tr>
<td>surrounding cellulitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- An elderly female nursing home resident WITHOUT A FOLEY becomes confused and her urine smells bad. The NA, per protocol, obtains a urine analysis and has 5-10 white blood cells and 48 hours later grows greater than 100,000 E. Coli. The resident returns to baseline mental status in 24 hours and she advises that she has no dysuria.

- What is the proper course of action?
  a. Recommend ciprofloxacin 250mg PO BID x14 days immediately (at onset of confusion)
  b. Wait until urine culture results return and decide on antibiotic course of therapy pending susceptibility results
  c. Recommend cranberry supplements to prevent E.coli UTIs in the future, treatment of this urine culture is optional
  d. Recommend no treatment and reassessment of institution’s protocol regarding urine culture practices
Does this patient have a UTI?

* Signs and symptoms usually associated with UTI are frequently absent in the catheterized patient. Foul smelling and/or cloudy urine is not a reliable indicator of infection and should NOT be an indication alone for testing the urine or starting antimicrobial therapy.

- Residents with intermittent or condom catheters are at lower risk for UTI and should be considered in the same risk category as those with no indwelling catheter.
- Catheter specimens should be collected following replacement of the catheter if the current catheter has been in place >14 days.
- Diagnosis of UTI in the catheterized patient should always be a diagnosis of exclusion in the absence of localized urinary tract findings.


Make sure to go to Anna Eslinger talk on When to Test presentation!!!
OVERVIEW

• Antibiotic mechanisms of action

• Antibiotic resistance

• How to select an antibiotic

• Common infectious disease treatments

• Antibiotic monitoring and common adverse reactions
### COMMON ADVERSE REACTIONS BY CLASS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Common side effects</th>
<th>Serious side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lactam (PCNs, ceph, carbapenems)</td>
<td>Hypersensitivity, rash, GI (N/V/D), <em>Clostridium difficile</em></td>
<td>Bone marrow suppression, acute interstitial nephritis</td>
</tr>
<tr>
<td>Fluoroquinolones (ciprofloxacin/levofloxacin)</td>
<td>Headache, rash, GI (N/V/D), insomnia, dizziness</td>
<td><em>Clostridium difficile</em>, MDR superinfections, tendonitis, CNS effects, QTc prolongation, glucose dysregulation</td>
</tr>
<tr>
<td>Aminoglycosides (Tobramycin, gentamicin)</td>
<td>Dizziness, GI (N/V/D)</td>
<td>Nephrotoxicity, ototoxicity, MDR superinfections</td>
</tr>
<tr>
<td>Vancomycin (IV)</td>
<td>Infusion reaction (rash, hypotension) <em>Clostridium difficile</em></td>
<td>Nephrotoxicity, neutropenia, MDR superinfections, DRESS</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Chest pain, edema, insomnia, pruritis, <em>Clostridium difficile</em></td>
<td>Eosinophilic pneumonia, myopathy</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Headache, GI (N/V/D), hepatic</td>
<td>Myelosuppression, serotonin syndrome (w/SSRI)</td>
</tr>
<tr>
<td>Oritavancin/Dalbavancin</td>
<td>Edema, headache, GI (N/V/D)</td>
<td>Infusion reactions</td>
</tr>
<tr>
<td>Trimethoprim/SMX</td>
<td>CNS and hematologic effects, TTP <em>Clostridium difficile</em></td>
<td>Hypersensitivity, hypoglycemia, hyperkalemia</td>
</tr>
<tr>
<td>Macrolides (azithromycin, clarithromycin)</td>
<td>GI (N/V/D), rash, abdominal pain, hepatic changes</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Urine discoloration, rash</td>
<td>Hemolytic anemia (pregnancy contraindication), pulmonary fibrosis</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Headache, GI (N/V/D)</td>
<td></td>
</tr>
</tbody>
</table>

This list is not exhaustive. Please consult drug reference for full list of adverse drug reactions and warnings.

### ANTAGONISTS 101

**Thank You!**

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