ANTIBIOTICS 101

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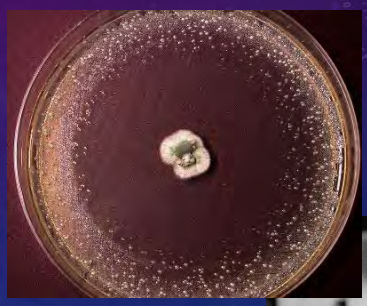
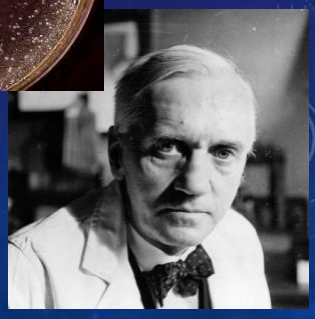
A BRIEF HISTORY OF ANTIBIOTICS – THE DISCOVERY OF PENICILLIN

- 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

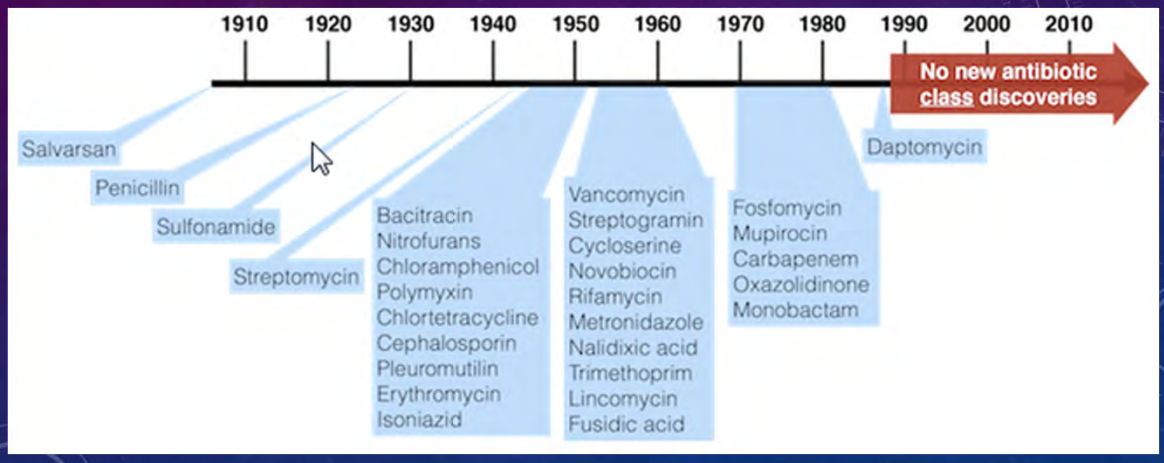
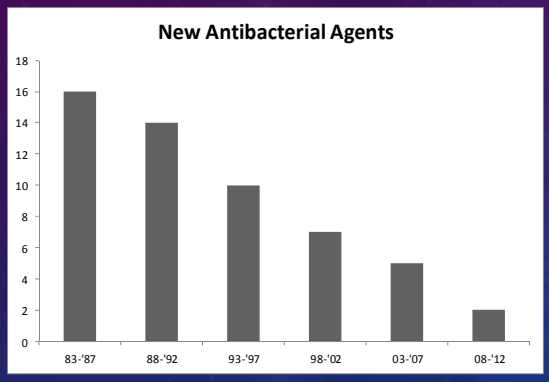


Image from www.khanacademy.org

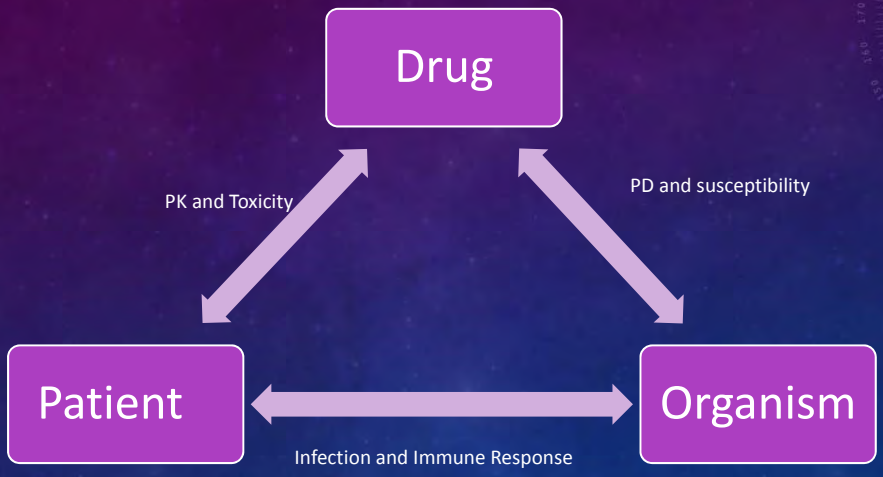
WHY SO MUCH INTEREST IN ANTIBIOTICS?

Antibiotics are a limited resource!



Antibiotic resistance is a world health issue!

ANTIBIOTICS ARE HARD!

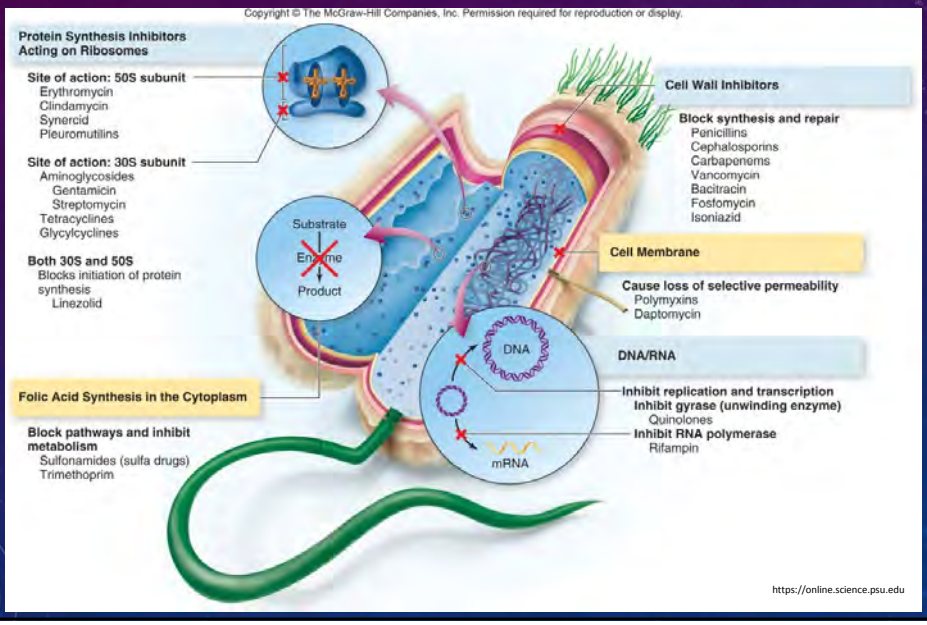


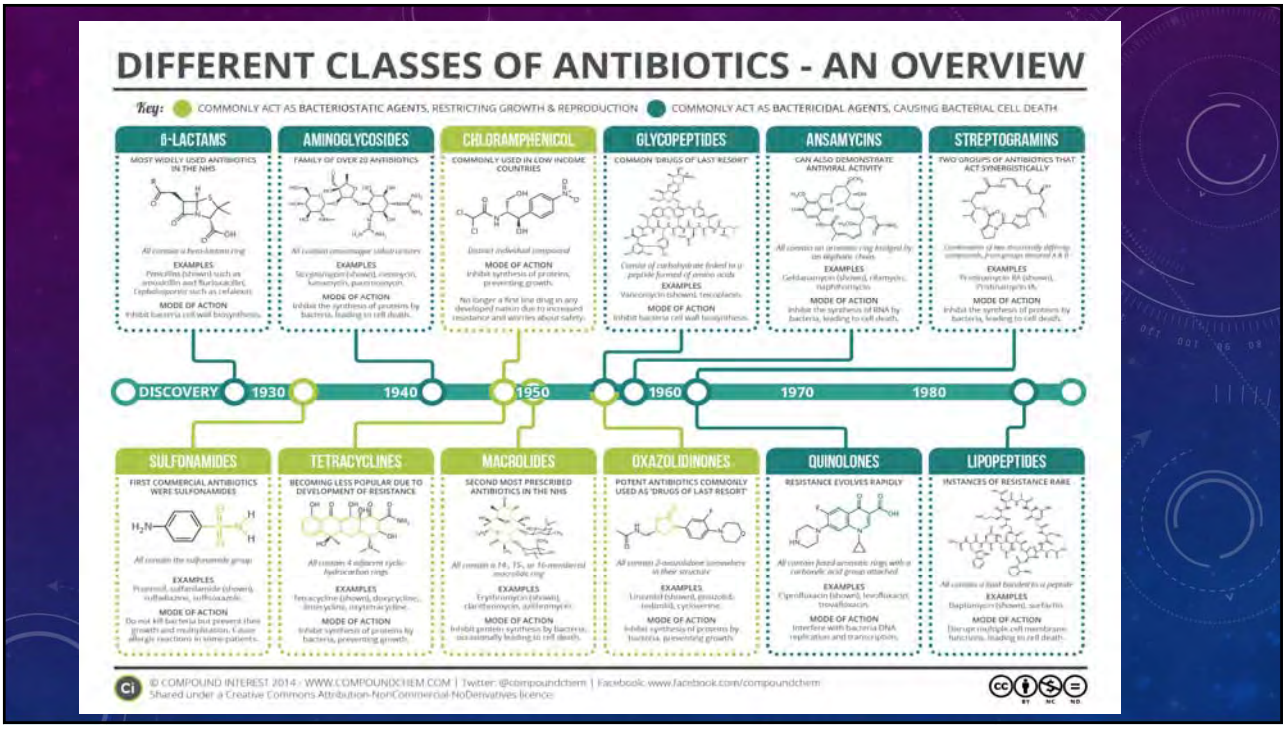
- PK is what the body does to the drug
- PD is what the drug does to the organism and body

OVERVIEW

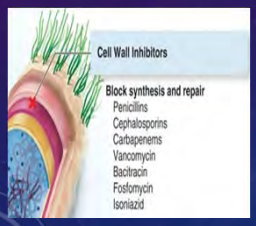
- Antibiotic mechanisms of action
- Antibiotic Resistance
- How to select an antibiotic
- Common infectious disease treatments
- Antibiotic monitoring and common adverse reactions

HOW DO ANTIBIOTICS WORK?



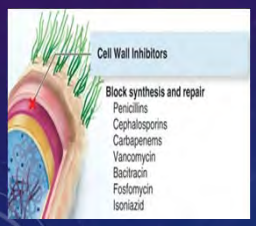


PENICILLINS – NARROW SPECTRUM



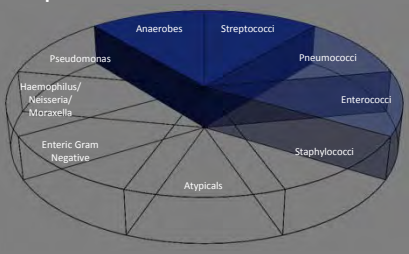
- Gram-positive activity
  - Natural: Penicillin (PCN) IV (PenG) or PO (PenVK)
    - Spectrum: Streptococcus, gram-positive anaerobes
    - Use: Dental prophylaxis, syphilis
  - PCNase-resistant: Nafcillin (IV), Oxacillin (IV), Dicloxacillin (PO)
    - Spectrum: Methicillin-Sensitive Staph. Aureus (MSSA)
    - 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



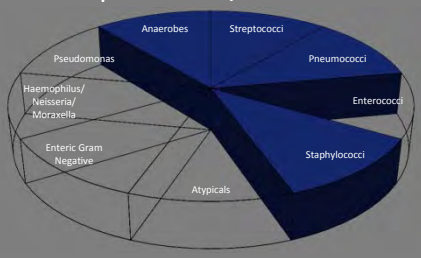
- Gram-positive, gram-negative, anaerobes
  - Extended Spectrum PCN: Piperacillin, Ticarcillin (IV)
    - Spectrum: Gram-negative organisms, Pseudomonas
    - Use: Rarely used without beta-lactamase inhibitors
  - Amp/sulbactam (Unasyn IV) or Amox/clavulanic acid (Augmentin PO)
    - Spectrum: Streptococcus, 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

Narrow Spectrum - PCN



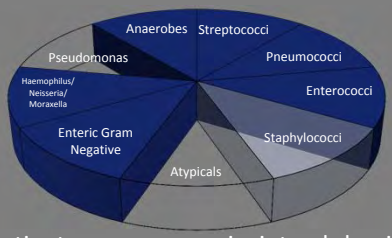
Outpatient use: dental prophylaxis, syphilis

Narrow Spectrum – Oxa/Nafcillin



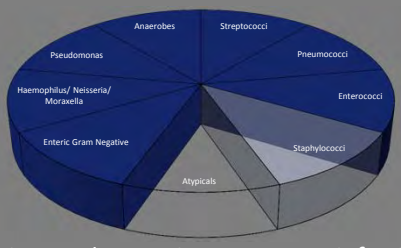
Inpatient and outpatient use: endocarditis, cellulitis

Ampicillin/sulbactam spectrum



Inpatient use: pneumonia, intraabdominal

Piperacillin/tazobactam spectrum



Inpatient and outpatient use: most infections

CEPHALOSPORINS

1st Generation **2nd Generation** **3rd Generation** **4th Generation**

***Not Ceftazidime**

Anaerobes

MSSA Coverage

Streptococcus

Gram Negative Coverage

NO ENTEROCOCCUS or MRSA COVERAGE… yet

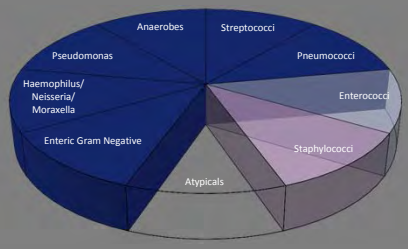
CEPHALOSPORINS

- 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

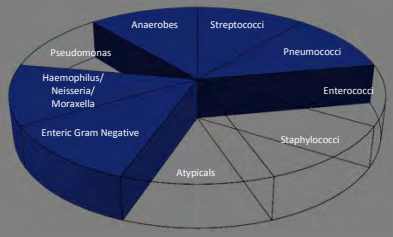
CARBAPENEMS – DRUGS OF LAST RESORT (OFTEN)

- 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

Meropenem/Imipenem/Doripenem Spectrum



Ertapenem Spectrum =
meropenem – Pseudomonas OR ampicillin/sulbactam - enterococci



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%)

1. MacLaughlin EJ, et al. Arch Fam Med 2000;9:722-6
2. Sade K, et al. Clin Exp Allergy 2003;33:501-6
Macy E et al. *J Allergy Clin Immunol*. 2014;133(3): 790-796

HOW CAN YOU HELP YOUR RESIDENTS?

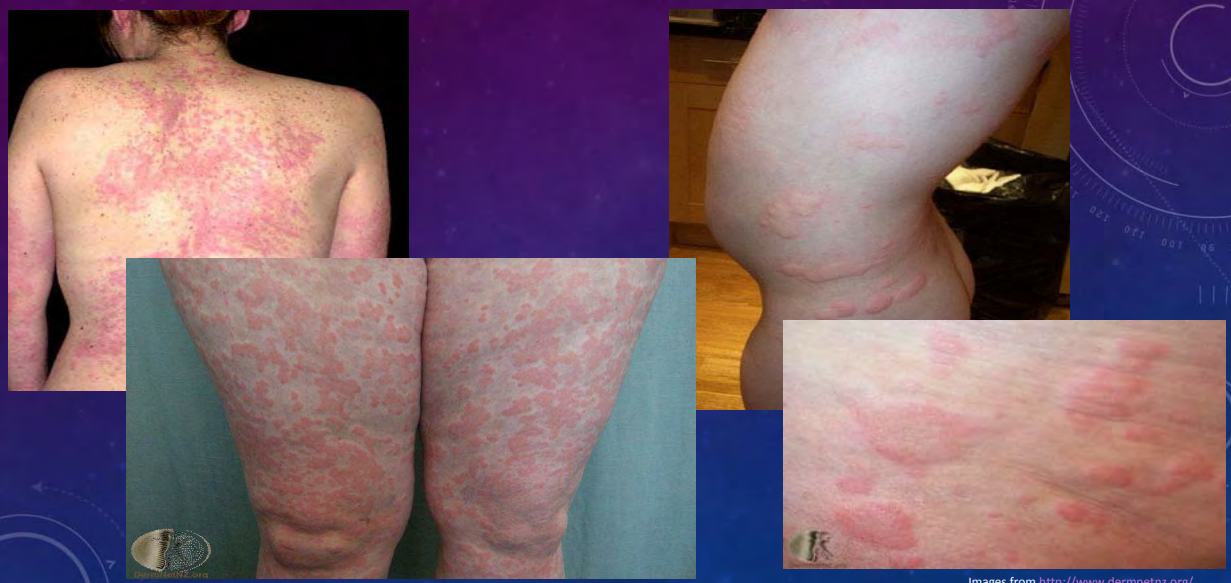
- **When did it happen?**
  - Age at the time of the reaction
  - Time of onset of the reaction after beginning the medication
  - Indication for medication – concurrent medications? Concurrent viral infection?
  - **Family history of allergy is not significant!**
- **What happened?**
  - Signs/symptoms 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.

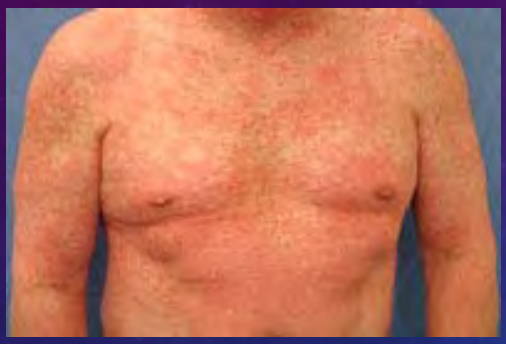
URTICARIAL RASH – IGE-MEDIATED

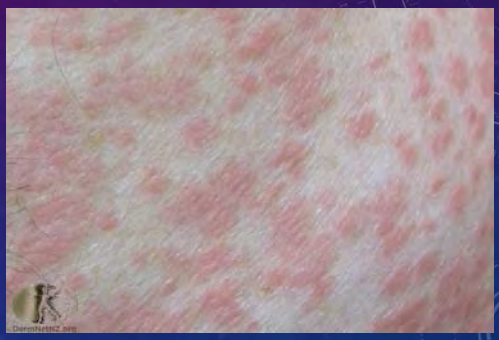


intensely pruritic, circumscribed, raised and erythematous eruption with central pallor

Images from http://www.dermnetnz.org/
http://www.allergy-clinic.co.uk/

MACULAR PAPULAR OR MORBILLIFORM RASHES – NON-IGE MEDIATED





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

Images from http://www.dermnetnz.org/

AVOID ANTIBIOTIC OF SAME/SIMILAR CLASS IF PATIENT REPORTS…

- IgE-mediated reaction *within* 24 hours of receiving
  - Immediate urticarial rash
  - Angioedema
  - Anaphylaxis
- Severe, non-IgE-mediate 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%[1]
  - Cephalothin and cephaloridine share side chain with penicillin
  - Contamination prior to GMP
  - Confounding by inclusion of nonallergic ADRs[2]
- Advent of 2nd, 3rd, 4th generation cephs[3]
  - Do not share a side chain
  - Rate of rashes from cephalosporins = 1-3%
- Cross reactivity rate between PCN and cephs <1% if using 2nd or 3rd gen ceph[4]

1. Bernstein IL, et al. Executive summary of disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999;83:665-700
2. Robinson JL, Hameed T, Carr S. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. Clin Infect Dis. 2002;35:26–31.
3. Depestel DD, Benninger MS, Danzinger L, et al. Cephalosporin use in treatment of patients with penicillin allergies. *J Am Pharm Assoc* 2008;48:530-40
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. 2010;105(4):259-273

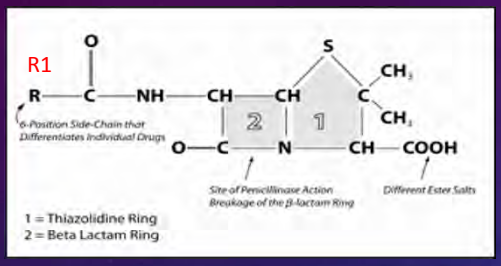
CROSS REACTIVITY WITH CARBAPENEMS

- 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

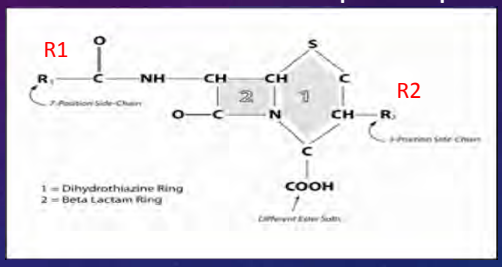
1. Prescott WA, Kusmierski KA. Clinical importance of carbapenem hypersensitivity in patients with self-reported and documented penicillin allergy. *Pharmacotherapy* 2007;27:137-42.
2. Prescott WA, DePestel DD, Ellis JJ, et al. Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *CID* 2004;38:1102-7.
3. Sodhi M. Is it safe to use carbapenems in patients with a history of allergy to penicillin? *JAC* 2004;54:1155-7.
4. Levitron I. Separating fact from fiction: the data behind the allergies and side effects caused by penicillins, cephalosporins, and carbapenem antibiotics. *Curr Pharmaceutical Design* 2003;9:983-8.
5. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009;43:304-15.
6. McConnell SA, Penzak SR, Warmack TS, Anaissie EJ, Gubbins PO. Incidence of imipenem hypersensitivity reactions in febrile neutropenic bone marrow transplant patients with a history of penicillin allergy. *Clin Inf Dis* 2000;31:1512-4

SIDE CHAINS

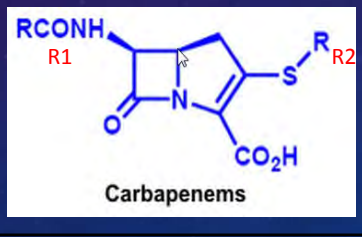
Chemical structure of penicillin



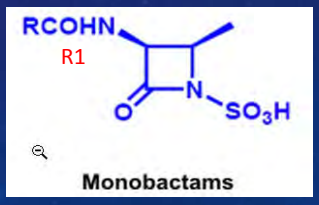
Chemical structure of cephalosporin



Chemical structure of carbapenem



Chemical structure of aztreonam

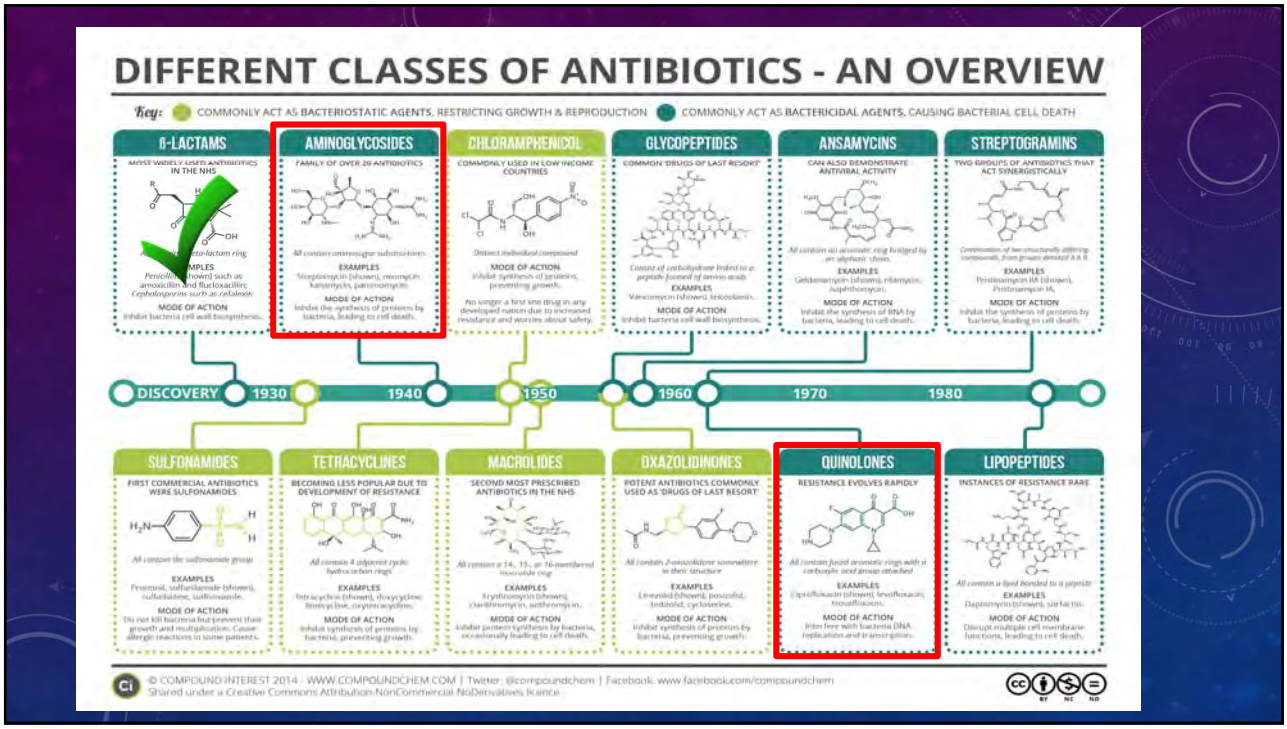


Images from J Am Pharm Assoc (2003). 2008;48(4):530-540. doi:10.1331/JAPhA.2008.07006 and http://www.chem.ox.ac.uk/

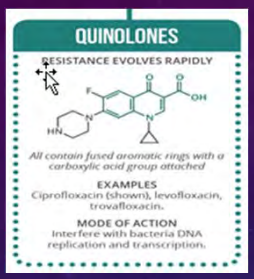
FDA-APPROVED BETA-LACTAM ANTIBIOTICS WITH SIMILAR SIDE CHAINS[A]

Agent	Agents with Similar Side Chains				
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil[c]	Cefprozil[c]	Cephalexin
Ampicillin	Amoxicillin	Cefaclor[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Aztreonam[b]	Ceftazidime[c]				
Cefaclor	Amoxicillin	Ampicillin[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Cefadroxil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefprozil[c]	Cephalexin
Cefdinir	Cefixime[d]				
Cefditoren	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	
Cefepime	Cefditoren[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefixime	Cefdinir[d]				
Cefotaxime	Cefditoren[c]	Cefepime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefoxitin	Cefuroxime[d]	Penicillin G			
Cefpodoxime	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Ceftriaxone[c]	Ceftaroline
Cefprozil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefadroxil[c]	Cephalexin
Ceftaroline	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Ceftazidime	Aztreonam[c]				
Ceftriaxone	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftaroline
Cefuroxime	Cefoxitin[d]				
Cephalexin	Amoxicillin	Ampicillin[c]	Cefaclor[c]	Cefadroxil	Cefprozil
Penicillin G	Cefoxitin				

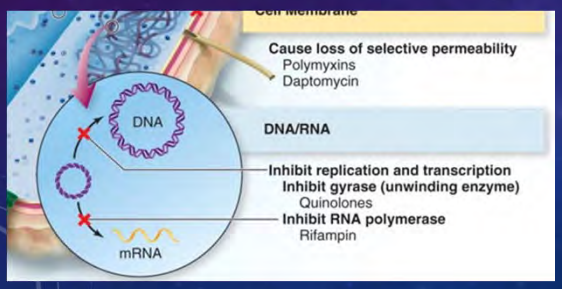
[a]Agents not listed are either not approved for use in the United States (ceftizoxime, ceftibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin)
[b]Aztreonam only cross-reacts with ceftazidime, with which it shares an identical side-chain
[c]Identical R1 side chain
[d]Identical R2 side chain



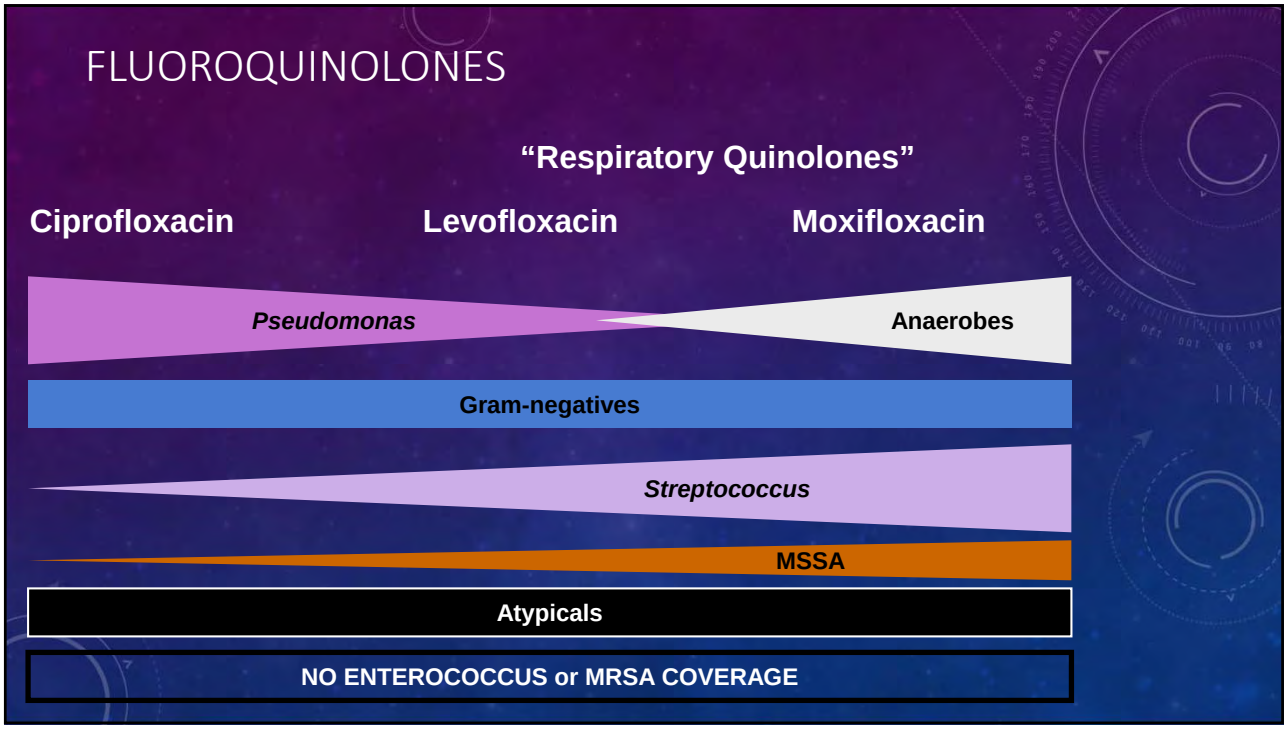
FLUOROQUINOLONES



- Ciprofloxacin, Levofloxacin, Moxifloxacin
- MOA: Inhibit DNA gyrase and topoisomerase, enzymes required for replication



FLUOROQUINOLONES



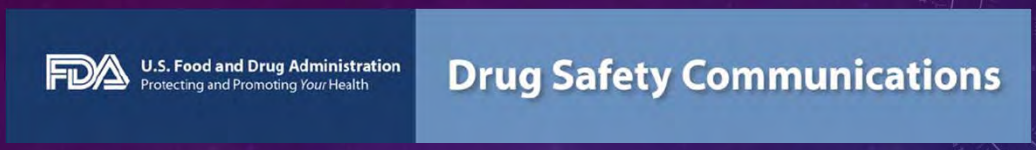
FLUOROQUINOLONES

- 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

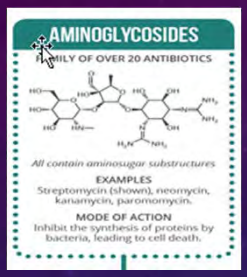
- QT prolongation → Cardiac Arrhythmias
- Tendon rupture (especially children and beagles)
  - Not FDA approved for children < 18 years old
- Sun-sensitivity
- Central Nervous System (CNS) side effects
- Super-infections
  - *Clostridium difficile*
  - Resistant gram-negatives
  - MRSA
- Many drug interactions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

FLUOROQUINOLONE FDA WARNING!

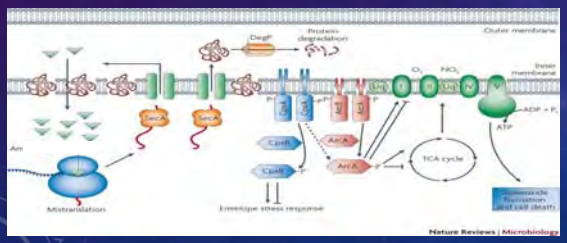


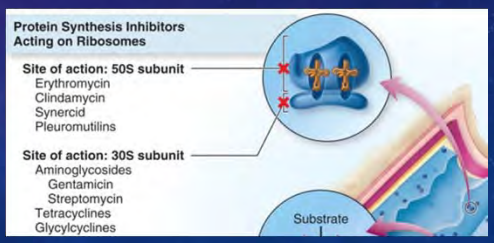
- Serious side effects associated with FQ outweigh the benefits of FQ use
- Fluoroquinolones are the drugs of last resort for acute sinusitis, acute bronchitis, and UTI
- Reserve FQ use for patients who do not have alternative treatment options

AMINOGLYCOSIDES



- Gentamicin, Tobramycin, Amikacin, Streptomycin
- MOA: Inhibit 30S subunit of the ribosome, ultimately inhibiting protein synthesis

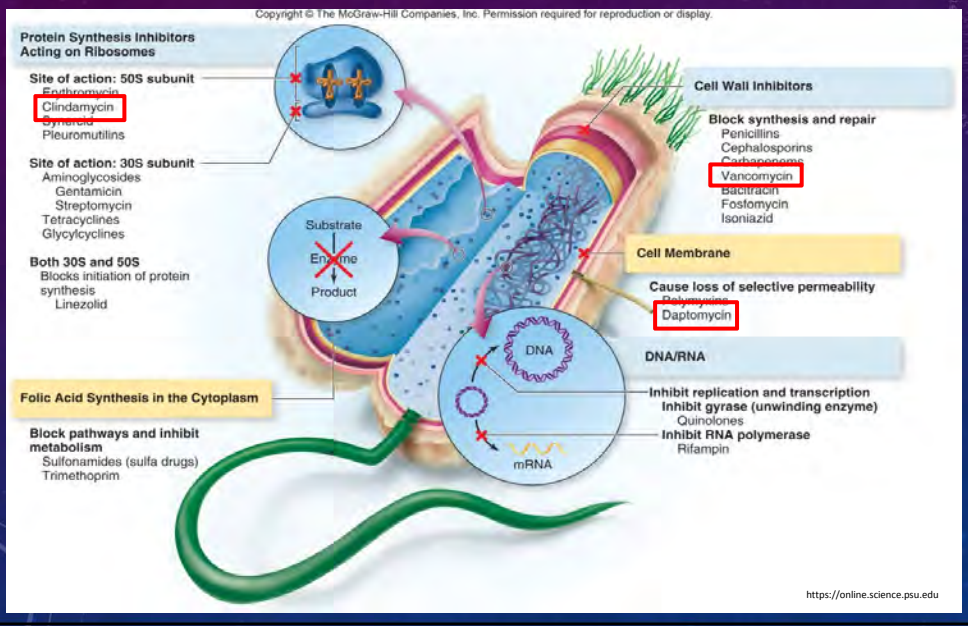




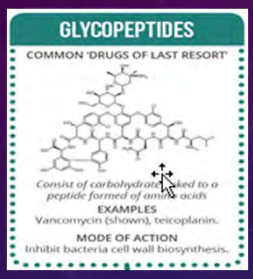
AMINOGLYCOSIDES

- 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)

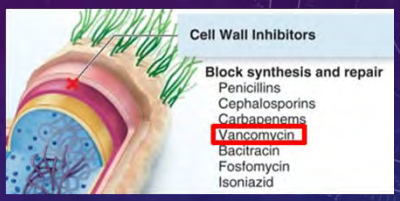
HOW DO ANTIBIOTICS WORK? – GRAM POSITIVES!

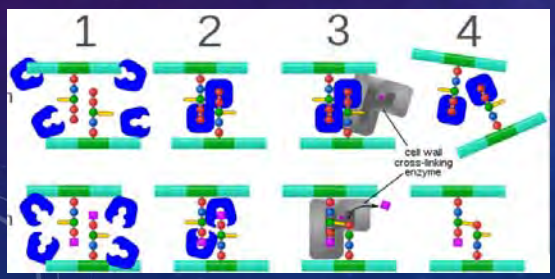


GLYCOPEPTIDES - VANCOMYCIN



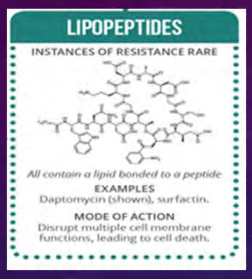
- Vancomycin (IV and PO)
  - PO for *Clostridium diffcille* only!
- MOA: Inhibit cell wall synthesis

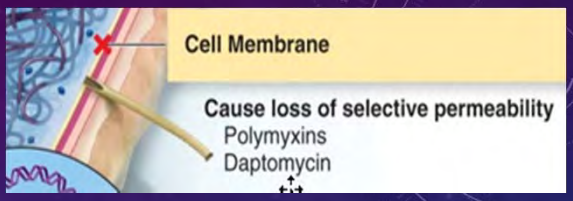




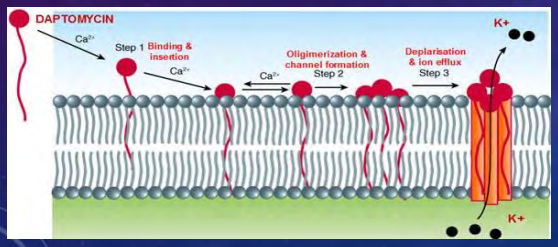
- Pros
  - Old drug, well studied
  - Multiple daily doses
  - Active against most Gram-positive organisms
  - Inexpensive
- Cons
  - Only IV available
  - Acute kidney injury
  - "Narrow" therapeutic index
  - Monitoring needed

LIPOPEPTIDES - DAPTOMYCIN



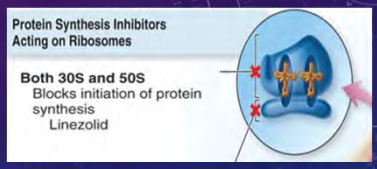


- Daptomycin (IV)
- MOA: Disrupt cell wall integrity and allows escape of intracellular components

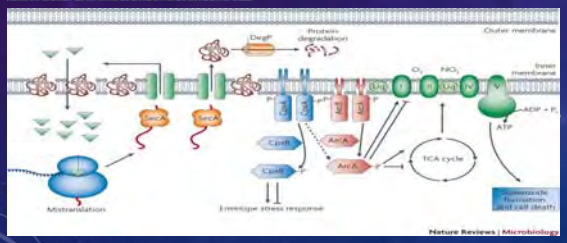


- Pros
  - Once daily dosing
  - Active against most Gram-positive organisms
  - Relatively safe
  - No serum drug concentration monitoring
- Cons
  - Expensive
  - Only IV available
  - Muscle toxicity

OXAZOLIDINONES - LINEZOLID



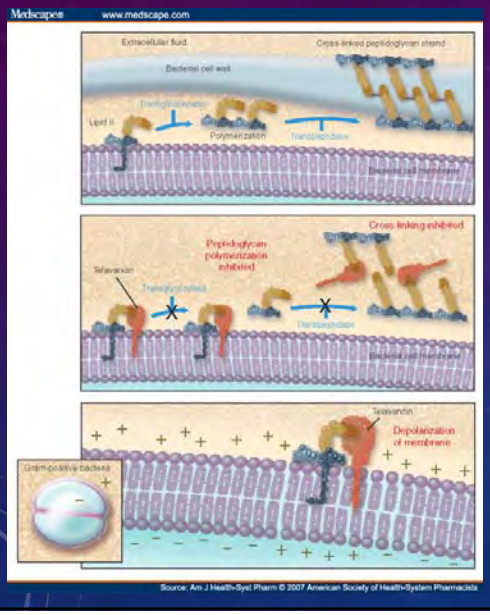
- Linezolid (IV and PO), Tedizolid (PO)
- MOA: Inhibit protein synthesis



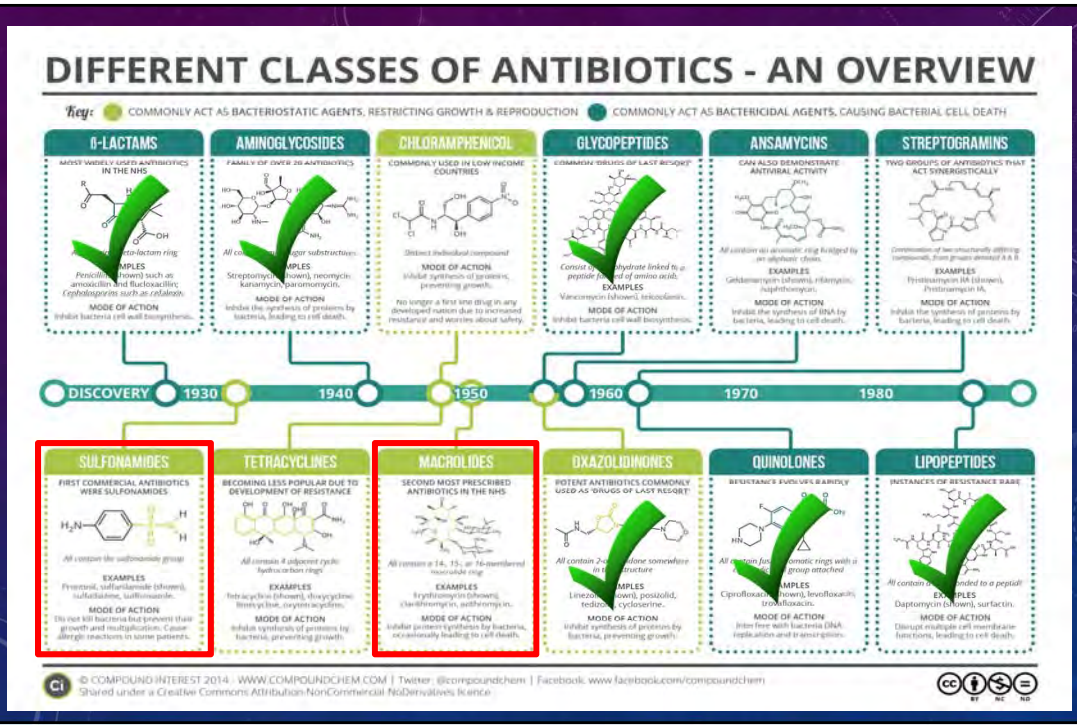
- Pros
  - Oral drug with good bioavailability
  - Active against most Gram-positive organisms
  - No serum drug concentration monitoring

Cons
- Leukopenias with long-term therapy
- Appropriate for severe disease?
- Expensive – sort of.

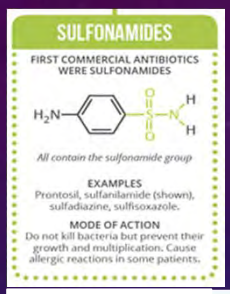
LIPOGLYCOPEPTIDES – TELAVANCIN, ORITAVANCIN, DALBAVANCIN



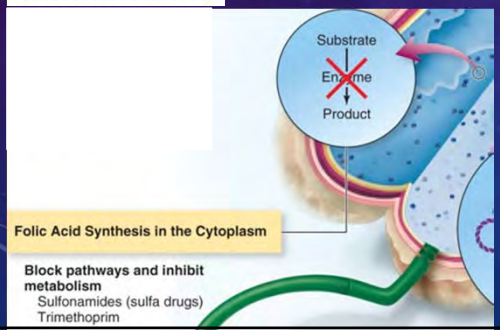
- Two mechanisms of action!
  - Transglycosidation and transpeptidation
- Pros
  - Once weekly dosing possible (orita and dalba)
  - Low risk for resistance development
  - Well tolerated
- Cons
  - EXPENSIVE!!!
  - New agents, not extensively studied
  - Use outside of acute bacterial skin and skin structure infections is limited



SULFONAMIDES – TMP/SMX OR BACTRIM

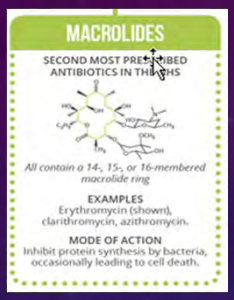


- Trimethoprim/sulfamethoxazole (IV and PO)
- MOA: Prevent important bacterial metabolic pathway

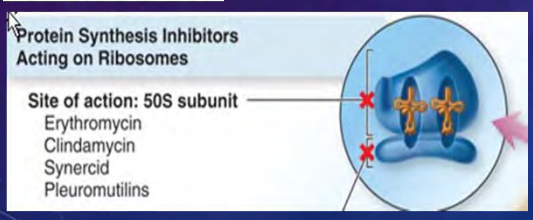


- Pros
  - Old drug, well studied
  - Oral drug with good bioavailability
  - Active against broad spectrum of bacteria
  - No serum drug concentration monitoring
- Cons
  - Inexpensive
  - Increasing rates of resistance, especially in urine
  - Rash is common
  - Photosensitivity and anemia

MACROLIDES – AZITHROMYCIN, ERYTHROMYCIN, CLARITHROMYCIN

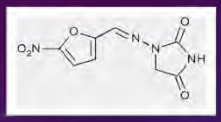


- Azithromycin (IV and PO), erythromycin (PO), clarithromycin (IV and PO)
- MOA: Inhibit protein synthesis



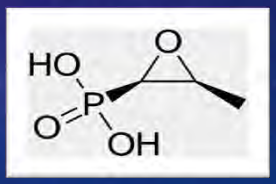
- Pros
  - Oral drugs with good bioavailability
  - Active against broad spectrum of bacteria
  - No serum drug concentration monitoring
- Cons
  - Inexpensive
  - Increasing rates of resistance
    - Erythromycin ineffective
  - Commonly cause GI upset

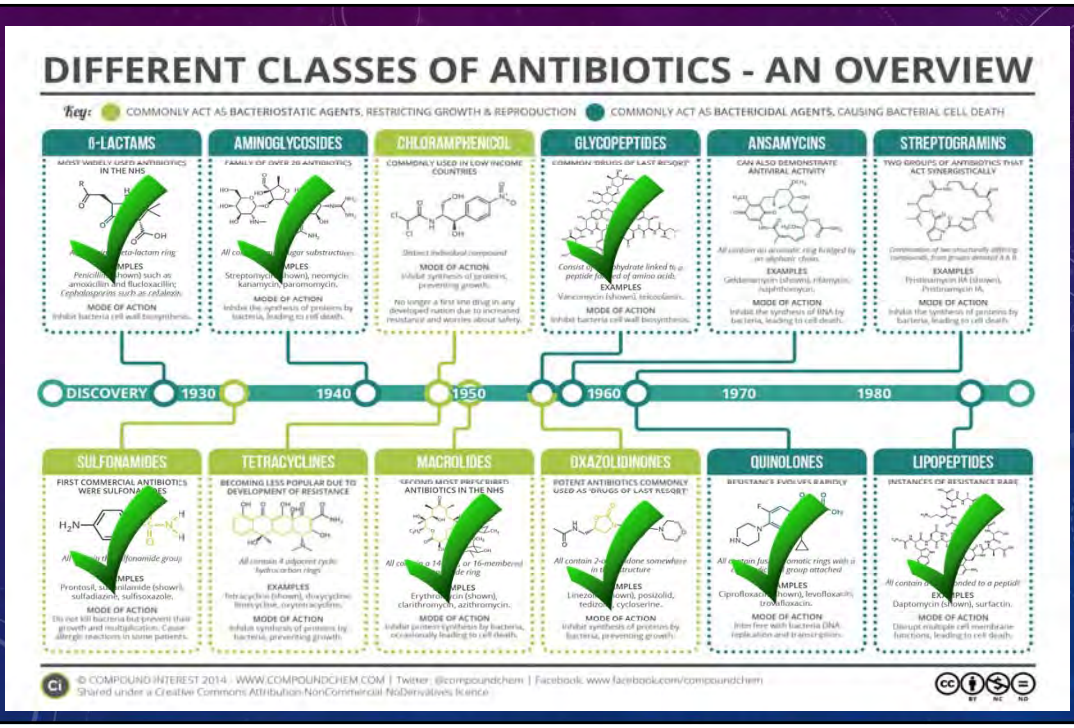
URINE AGENTS!



- 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



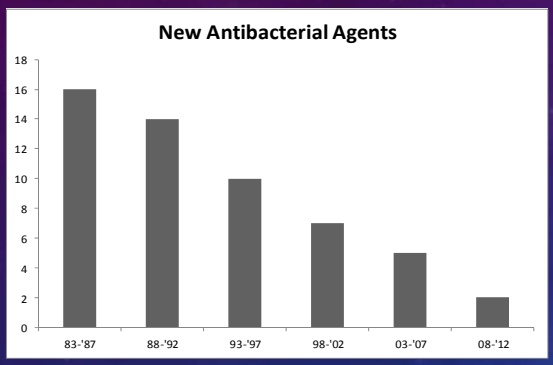


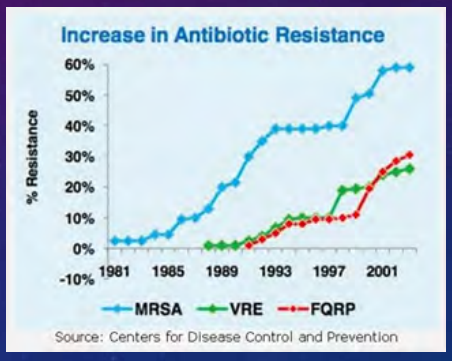
OVERVIEW

- 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!





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

Clin Infect Dis. (2010) 50 (8):1081-1083.

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

CDC Antibiotic Resistance Threats in the United States, 2013

ANTIBIOTIC RESISTANCE IS REAL

Antibiotic Resistance and Superbugs, (
of Dangers

Added by Natalia Sanchez on March 5, 2014.

Can We Stop the End of Effective Antibiotics?

To check the advance of antibiotic resistance, we've got to get smarter about dispensing drugs

CDC calls on hospitals, doctors to fight antibiotic resistance

CAN WE WIN?????

BY J

Posted: Feb 10, 2014 3:26 PM CST
Updated: Feb 17, 2014 3:44 PM C

By: Jay Dillon, Senior Digital Content Manager - email

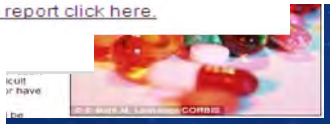
It's a problem causing 23,000 deaths a year. Doctors say there are infections out there that can no longer be cured by the antibiotics we have to treat them.

The term for this scary reality is antibiotic resistance. It's not only causing deaths, but it's also costing the healthcare system and patients a lot of money. The CDC is calling on hospitals and physicians to do something, and Oklahoma is responding.

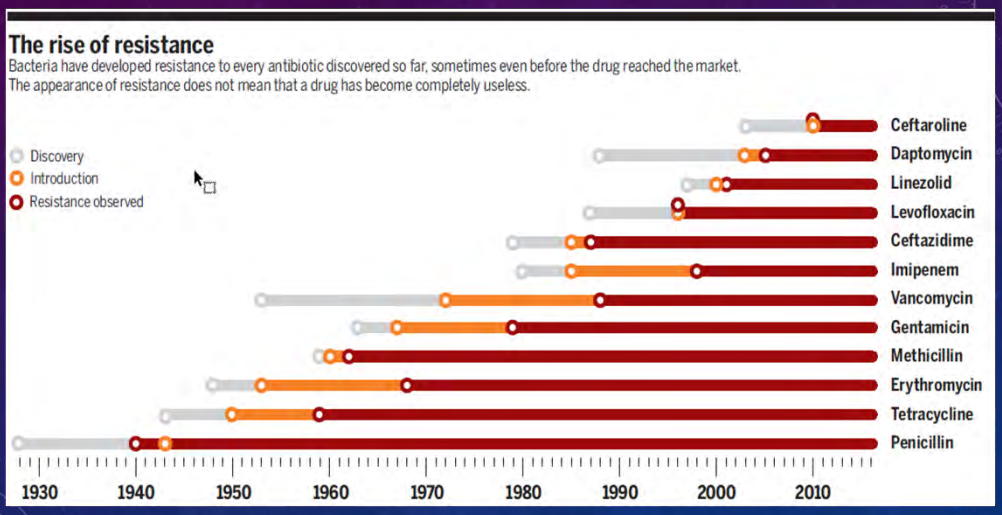
To see the full CDC Antibiotic Resistance Threats report click here.

One form of antibiotic-resistant bacteria, known as CRE, that kills about 600 people every year.

CREDIT: AP PHOTO/CENTERS FOR DISEASE CONTROL AND PREVENTION



NEW DRUGS, NEW RESISTANCE



Kupferschmidt K. Resistance fighters. Science. 2016 May 352 (6287): 758-761

CAUSES OF ANTIBIOTIC RESISTANCE

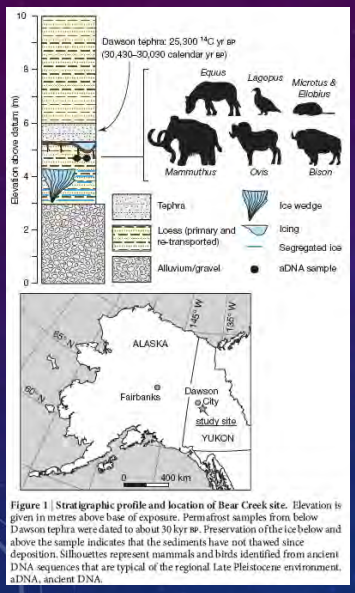
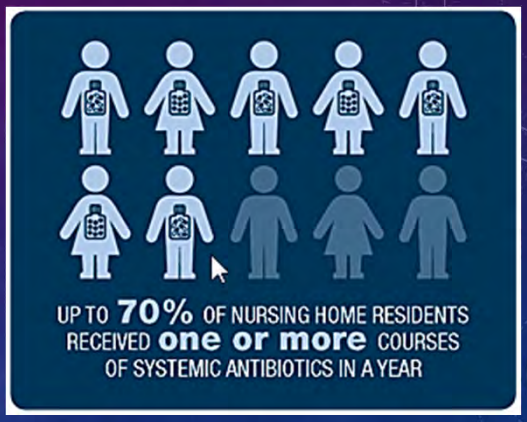
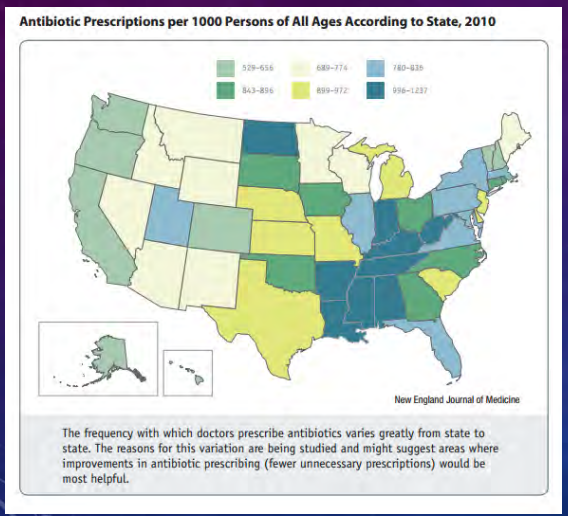


Figure 1 | Stratigraphic profile and location of Bear Creek site. Elevation is given in metres above base of exposure. Permafrost samples from below Dawson tephra were dated to about 30 kyr BP. Preservation of the ice below and above the sample indicates that the sediments have not thawed since deposition. Silhouettes represent mammals and birds identified from ancient DNA sequences that are typical of the regional Late Pleistocene environment. aDNA, ancient DNA.

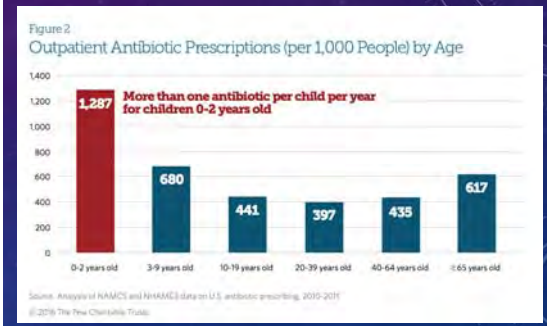


D'costa VM, et al. Antibiotic resistance is ancient. Nature 2011; 477: 457-461
CDC Core Elements of Antibiotic Stewardship in Nursing Homes

ANTIBIOTIC PRESCRIBING PATTERNS



The frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (fewer unnecessary prescriptions) would be most helpful.



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!

1. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159-177.
2. Lim CJ, Kong DCM, Stuart RL. Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives. Clin Interven Aging. 2014; 9: 165-177.
3. Nicolle LE, Bentley D, Garibaldi R, et al. Antimicrobial use in long-term care facilities. Infect Control Hosp Epidemiol 2000; 21:537–45

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

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

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

OVERVIEW

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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

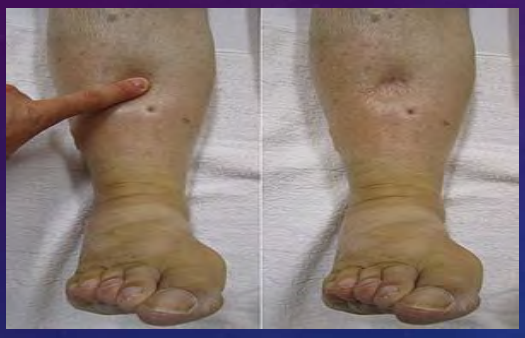
- Peripheral edema
- Erythema
- Warmth
- Tenderness
- "Orange peel" appearance
- Vesicles
- Bullae
- Petechiae
- Pain

Swartz MN. Clinical practice. Cellulitis. *N Engl J Med.* 2004;350(9):904-912.
Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10-52.
May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect (Larchmt).* 2009;10(5):467-499.
Bailey E, Kroshinsky D. Cellulitis: diagnosis and management. *Dermatol Ther.* 2011;24(2):229-239.

MYTH 1: ALL RED AND SWOLLEN SKIN IS CELLULITIS.

Common signs/symptoms

- Peripheral Edema



Alternative Peripheral Edema Causes

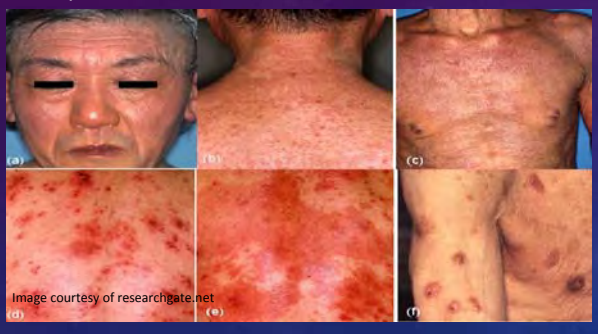
- Heart failure
- Cirrhosis (hypoalbuminemia)
- Primary renal sodium retention
  - Nephrotic syndrome
  - NSAIDs, glucorticoids, glitazones, hormone therapy, vasodilators, Ca^{++} channel blockers
- Fluid overload (parenteral therapy?)
- Venous thrombosis or stenosis
- Chronic venous insufficiency (post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

Swartz MN. Clinical practice. Cellulitis. *N Engl J Med.* 2004;350(9):904-912.
Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10-52.
May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect (Larchmt).* 2009;10(5):467-499.
Bailey E, Kroshinsky D. Cellulitis: diagnosis and management. *Dermatol Ther.* 2011;24(2):229-239.

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

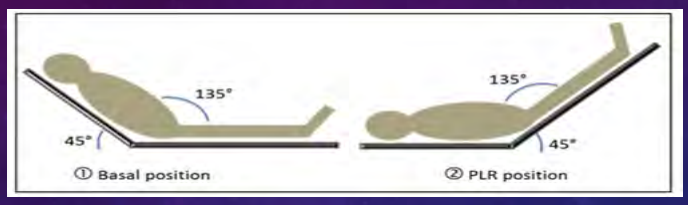
Swartz MN. Clinical practice. Cellulitis. *N Engl J Med.* 2004;350(9):904-912.
Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10-52.
May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect (Larchmt).* 2009;10(5):467-499.
Bailey E, Kroshinsky D. Cellulitis: diagnosis and management. *Dermatol Ther.* 2011;24(2):229-239.

MYTH 2: BILATERAL LEG SWELLING AND REDNESS IS CELLULITIS.

- Bilateral leg cellulitis is exceedingly rare
  - LE cellulitis commonly caused by breech 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

Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: part II. Conditions that simulate lower limb cellulitis. *J Am Acad Dermatol.* 2012;67(2):177.e171-179; quiz 185-176.
Hughey LC. The impact dermatologists can have on misdiagnosis of cellulitis and overuse of antibiotics: closing the gap. *JAMA Dermatol.* 2014;150(10):1061-1062.

PASSIVE LEG RAISE AND TREATMENT OF BILATERAL LE CELLULITIS



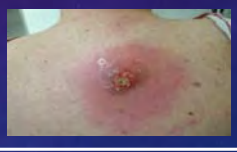
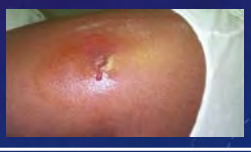
- Passive leg raise should alleviate erythema and swelling if non-infectious (promotes gravity drainage of edema and inflammatory substances)
- Treatment if non-infectious
  - Elevate affected area TID
  - Apply elastic bandages from toes to thighs q8hrs

SSTI – SITE OF INFECTION AND SOCIAL FACTORS

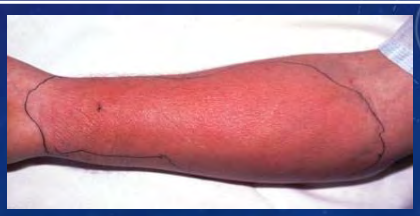
- What is the site of infection?
  - Size of the infection? I&D alone ok?
  - Abscess/Purulence present? More to come
  - Difficult to penetrate site? --- Not an issue with SSTI
  - Necrotizing infection? If yes, then needs surgery
- Social factors?
  - Ability to provide IV therapy?
  - Insurance coverage?
  - 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

Swartz MN. Clinical practice. Cellulitis. *N Engl J Med.* Feb 26 2004;350(9):904-912.
Lipsky BA, Armstrong DG, Citron DM, Tice AD, Morgenstern DE, Abramson MA. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP). *Lancet.* Nov 12 2005;366(9498):1695-1703.

SSTI – POTENTIAL ANTIBIOTIC THERAPY

	Intravenous Therapy	Oral Therapy
Streptococcus sp.	Penicillin	Amoxicillin
Streptococcus sp. and MSSA	Oxacillin/Nafcillin	Dicloxacillin
	Cefazolin	Cephalexin
	Clindamycin	Clindamycin
Streptococcus sp., MSSA and MRSA	Vancomycin	Trimethoprim/sulfamethoxazole PLUS *Streptococcus* drug
	Linezolid	
	Clindamycin	Doxycycline OR minocycline PLUS *Streptococcus* drug
	Daptomycin	
	Telavancin	Linezolid
	Ceftaroline	Clindamycin
	Oritavancin/Dalbavancin	

This list is not meant to be exhaustive and only serves as an example for the complexity of antibiotic decision making for the treatment of SSTI

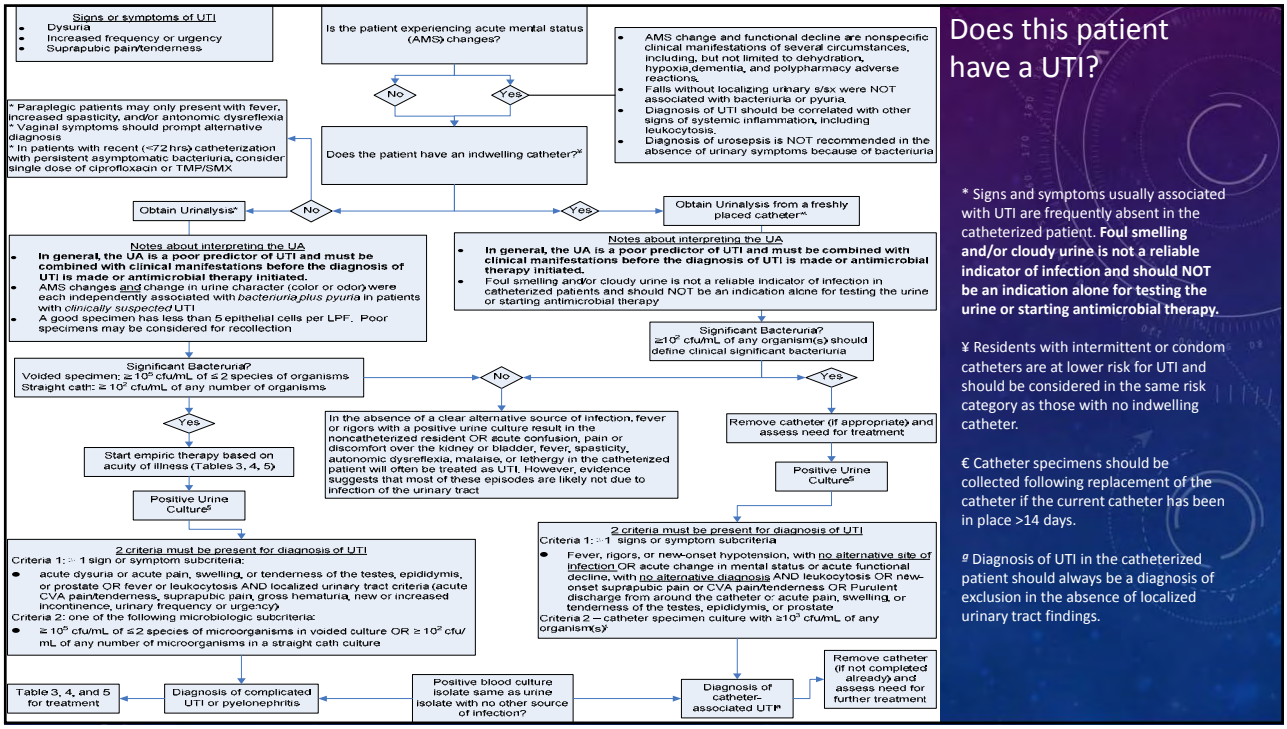
- What makes this patient unique?
  - Weight, Age, Sex, Allergies?

GENERAL PRINCIPLES – SELECTING AN ANTIBIOTIC

	Outpatient	Inpatient
No abscess	Cephalexin or Dicloxacillin	Cefazolin or Oxacillin
Abscess w/o surrounding cellulitis	I&D + TMP-SMX	I&D + Vancomycin
Abscess w/ surrounding cellulitis	I&D + TMP-SMX + Cephalexin	I&D + Vancomycin + Cefazolin

- 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



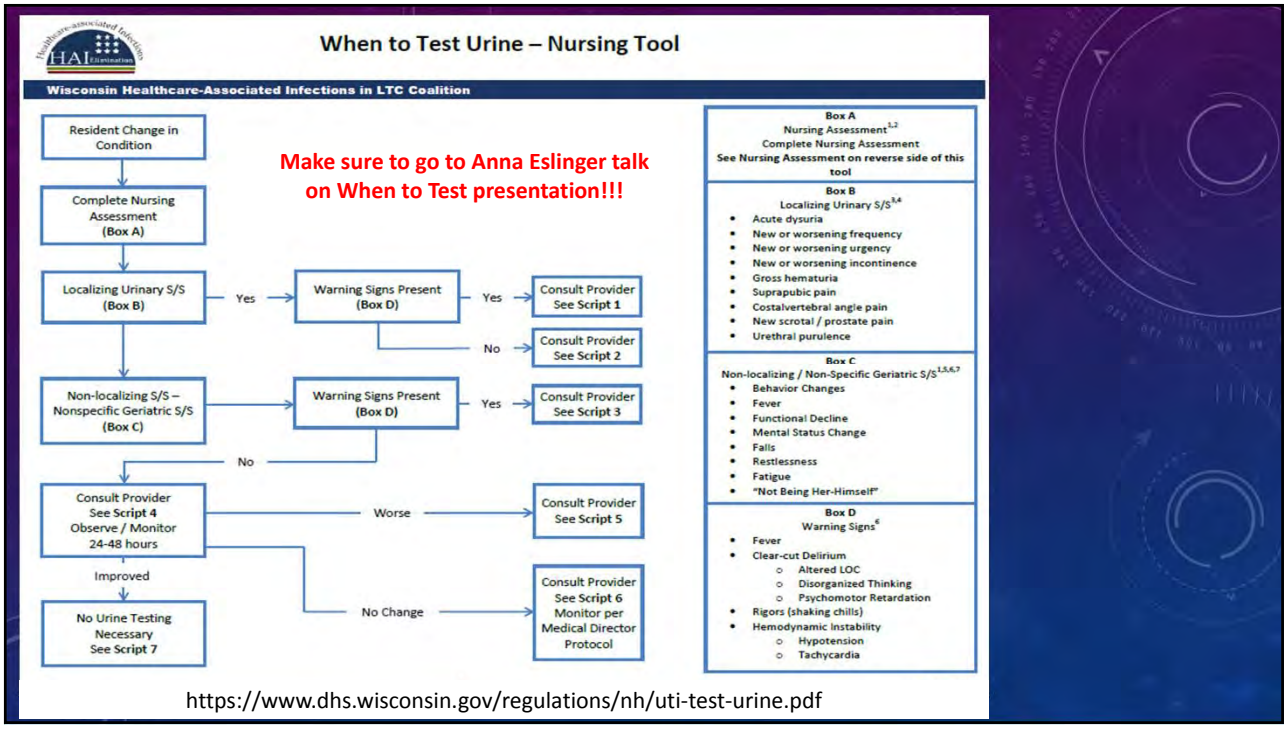
Does this patient have a UTI?

* 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.



https://www.dhs.wisconsin.gov/regulations/nh/uti-test-urine.pdf

ANTIBIOTIC TREATMENT OF URINARY TRACT INFECTIONS

		Drug	Dose and Duration	Notes
Uncomplicated UTI/cystitis	Empiric treatment	Nitrofurantoin	100mg PO BID x5 days	CrCl<30ml/min contraindicated CrCl 30-50 ml/min: use with caution and monitor for symptom resolution Not for use in pyelonephritis
		Trimethoprim/ Sulfamethoxazole [C]	160/800 mg PO BID x3 days	Caution is advised in patients received prophylaxis since likelihood of resistance is high
		Cefpodoxime [C,D]	100 mg PO BID x7 days	Consider change to narrow spectrum β-lactam when susceptibilities are known
		Ciprofloxacin/ levofloxacin [C]	Ciprofloxacin 250mg PO BID x3 days Levofloxacin 250mg PO daily x3 days	Caution is advised due to increased rates of resistance and risk of Clostridium difficile infection and other super-infections associated with fluoroquinolone use Moxifloxacin should not be used due to low urinary concentrations
	Definitive Treatment	Amoxicillin [C]	500 mg PO BID x7 days	Active against ampicillin-susceptible Enterococcus sp.
		Cephalexin [C,D]	500 mg PO BID x7 days	
		Fosfomycin	3gm PO x1	Susceptibility testing is limited; however, E.coli resistance rates are low Has in-vitro activity against VRE and ESBL producing bacteria Not for use in pyelonephritis
Pyelonephritis/ Complicated UTI		Ciprofloxacin	500mg PO BID x7-10 days	
		Levofloxacin	750mg PO BID x5 days or 500mg PO daily x7-10 days	
		Ceftriaxone	1gm IV q24 hours x 7 days	Easy to use IV alternative to fluoroquinolones
		Tobramycin/ Gentamicin	5mg/kg (adj BW) IV q24 hours x 7 days	Consider for patients with recent fluoroquinolone or β-lactam use

A These agents are listed in their preferred order. The optimal therapy depends on many factors and each medication has risks and benefits which must be considered when choosing treatment.
B Definitive therapy should be guided by susceptibility testing and results.
C Doses should be adjusted based on renal function. See *Renal Function-based Dose Adjustments – Adult – Inpatient Clinical Practice Guideline.*
D Cefdinir, Cefixime, Cefuroxime, or Cefpodoxime may be considered as alternative if necessary for insurance coverage or if for other clinical reason.

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

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

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

ANTIBIOTICS 101

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