Antibiotics:
What IPs should know in 2023 to be a good team player

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Orange County APIC

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Conflict of interest/bias/financial disclosure

- I have no conflict of interest to report in relation to the content of this presentation
- This presentation was created for the purpose of sharing information concerning antibiotic usage and bacterial resistance that is generally available and has been pulled from non-industry sources that are free of bias; any other content that I have personally added to place this information in context is likewise free of bias.
- Although I have had prior relationships with pharmaceutical entities in the process of performing clinical trials in years past, I currently do not have such active relationships financial or otherwise

Game plan

- Introduction/5-on-5 analogy?
- Review of antibiotics and their evolution
  - Role of resistance in antibiotic development and utilization
  - Pharmaceutical industry and the drug development process
  - How resistance occurs: plasmid vs chromosomal
- Review of specific antimicrobial classes and select agents
- Current terrain: MDROs, restricted abx, empiric use/de-escalation, order sets
- AS teamwork: shared goals/different roles (pharmacy, providers, RNs, lab, IP)
- Examples
- Questions

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5-on-5 ASP: Bugs vs. drugs / shirts vs. skins

- Two "teams": Bugs and Drugs
- "Starting 5s"
  - Bugs: Staph aureus, enteric GNRs, Pseudomonas, streptococcal spp, anaerobes
  - Drugs: "Basic" beta-lactams, vanco, quinolones, aminoglycosides, macrolides
- Bench players
  - Bugs: MRSA and other MDROs, enterococcus, Candida, atypicals, TB
  - Drugs: Carbapenems, tetracyclines, clinda/flagyl, antifungals, restricted agents
- Coach: HCP team* (responsible for in-game tactical decision-making)
- General manager: pharmacy (crafted team to best match opponent)
- Game situation: Time left? How aggressive should/can we be?

*HCP team: providers, bedside RNs, AS pharmacists, microbiology lab, IP

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Summary of antimicrobial class characteristics

Antimicrobial Class	1st agent discovered	General *bacterial* activity spectrum				Relative CDI risk	Allergy issues
		Gram(+)	Gram(-)	AnO2	Other*		
Beta-lactam agents	1928					Depends on agent	Moderate to high
Glycopeptides	1958		X		X	Low	Low to moderate
Quinolones	1962			X		High	Low to moderate
Aminoglycosides	1967	X		X		Low	Low
Tetracyclines	1945					Low	Low to moderate
Macrolides	1952			X		Low-Moderate	Low to moderate
Sulfonamides	1932			X		Low- Moderate	Moderate
Other antibacterial agents	1953					Depends on agent	Depends on agent
Antifungal agents	1949	X	X	X		n/a	Low
Antiviral agents	1963	X	X	X		n/a	Low
Anti-parasitic agents	1960	X	X	X		Low	Depends on agent

*Other: Mycobacteria, Mycoplasma, Nocardia, Rickettsiae, Spirochetes; fungi, viruses, parasites

Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, “red man” rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
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Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
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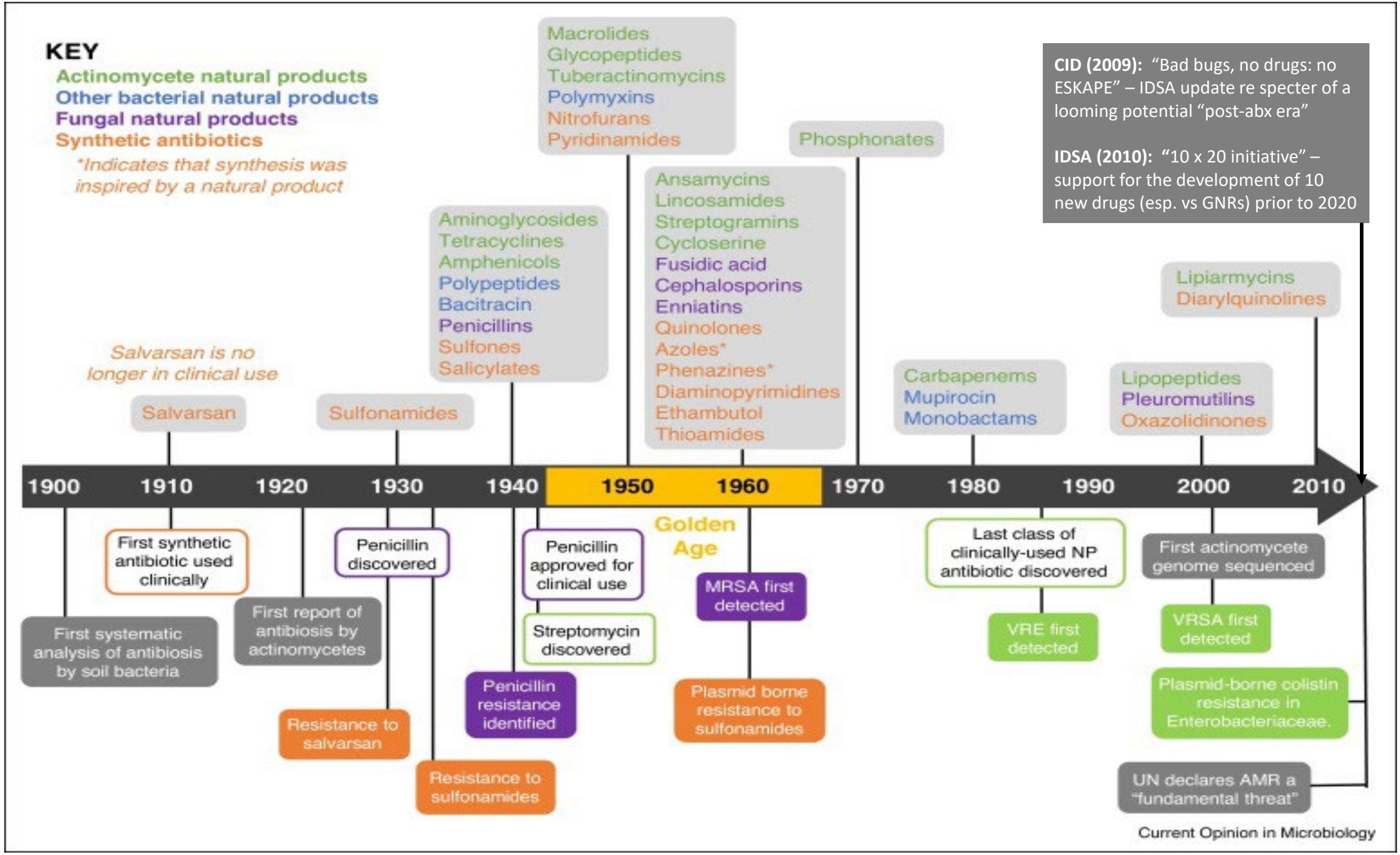
Anti-parasitic agents					Varies by agent	Low	Depends on agent

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✔	✔	✔	✔	✔	✔	✔	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✔			✔		✔		VRE (VanA, VanB)
Quinolones		✔	✔	✔			✔	DNA gyrase (gyr)
Aminoglycosides						✔	✔	
Tetracyclines	✔	✔				✔	✔	
Macrolides		✔					✔	Efflux pump
Sulfonamides	✔		✔	✔			✔	
Other antibacterial agents*	✔	✔		✔	✔	✔	✔	
Antifungal agents	✔	✔	✔		✔		✔	
Antiviral agents	✔	✔			✔		✔	
Anti-parasitic agents				✔	✔		✔	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example, TB/NTM, spirochetal, or rickettsial infections



CID (2009): "Bad bugs, no drugs: no ESKAPE" – IDSA update re specter of a looming potential "post-abx era"

IDSA (2010): **"**10 x 20 initiative" – support for the development of 10 new drugs (esp. vs GNRs) prior to 2020

2001 BC	Here, eat this root.
1000 AD	That root is heathen. Here, say this prayer.
1850 AD	That prayer is superstition. Here, drink this potion.
1920 AD	That potion is snake oil. Here, swallow this pill.
1945 AD	That pill is ineffective. Here, take this penicillin.
1955 AD	Oops... bugs mutated. Here, take this tetracycline.
1960-1999 AD	39 more "oops"... Here, take this more powerful antibiotic.
2000 AD	The bugs have won! Here, eat this root.

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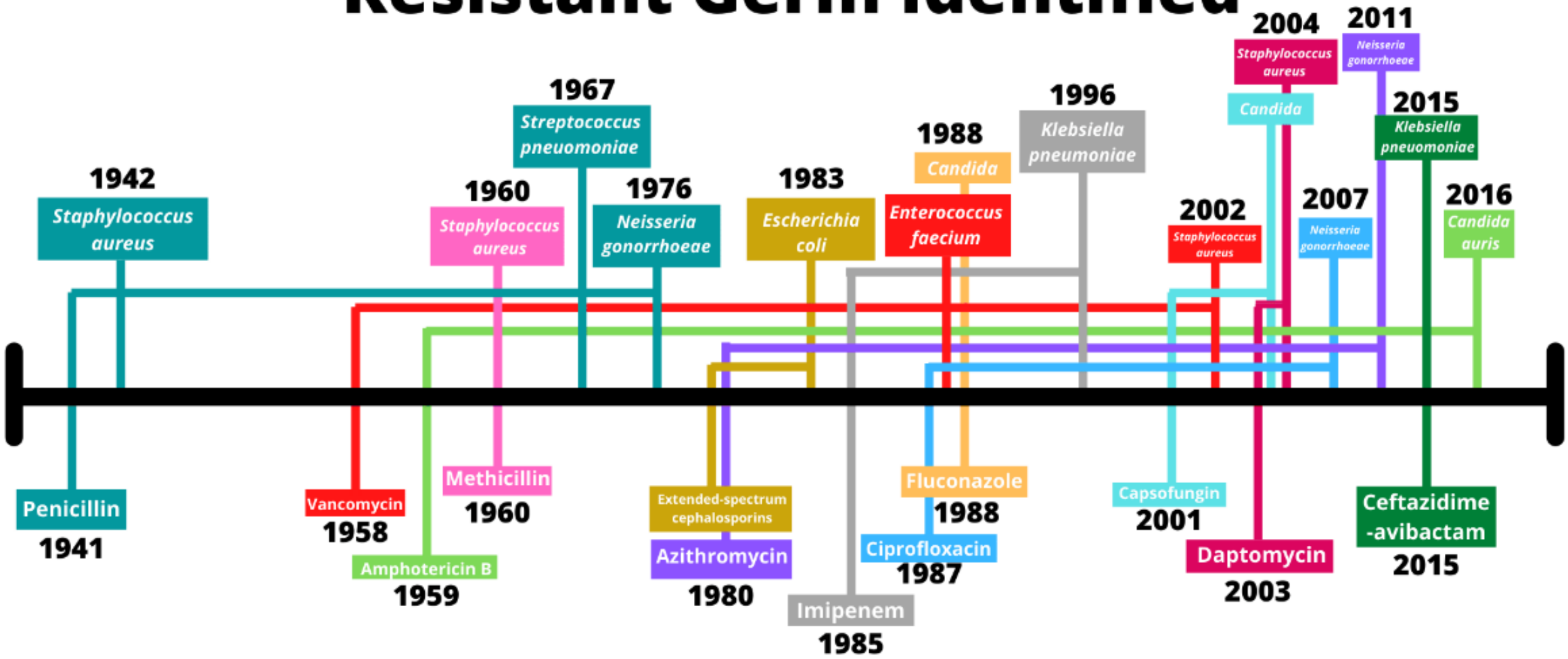
Resistant Germ Identified



Pharmaceutical industry and drug development

- Pharmaceutical INDUSTRY
  - Antibiotics are NOT big money-makers compared to treatments for chronic illness
    - Potentially curative agents utilized for relatively short periods of time
    - Effective revenue-generating "life" of an antibiotic limited by development of resistance
  - "Big Pharma": Profit-driven **business** accountable to shareholders
  - Smaller biotech companies on the rise as larger drug companies consolidate
  - Challenges/vulnerabilities of out-sourcing and non-domestic supply chain "links"
- Drug development process
  - Clinical trials
    - Phase I: safety and optimal dose (often <<100 subjects)
    - Phase II: effectiveness and side effects (may involve 100s of subjects)
    - Phase III: comparison of new drug with existing therapies (may involve 1000s of subjects)
  - FDA review/approval process
    - Phase IV: post-marketing continued data gathering

How resistance develops: "It takes *2* (conditions)"

- Mutation
  - A spontaneously-occurring **error** in exactly replicating the "parent" organism
  - Introduces **variation** into what would otherwise be a homogeneous population
  - Creates a dynamic (rather than a stagnate) situation where **selection** can occur
    - Mutations providing a survival advantage under **a certain set of circumstances** can potentially thrive
    - Mutations NOT providing any survival advantage will not be carried forward to future generations
- Selection
  - Introduction of an antibiotic to which a pathogen has become resistant via a mutation "favors" that pathogen as long as that antibiotic is in the pathogen's environment
  - The "favored" pathogen becomes predominant and perhaps clinically impactful
  - Absent the antibiotic to which it is resistant, the mutated pathogen would never have emerged as a threat

Types of resistance: location, location, location

- Chromosomal
  - Resistance gene [mutation] carried on bacterial chromosome
  - Transmitted (to progeny cells) via chromosomal replication/**bacterial cell division**
  - Limited potential for spread beyond current bacterial species, slow evolution
  - Example: quinolone resistance
- Plasmid-mediated
  - Resistance gene(s) carried on extra-chromosomal circular nucleic acid
  - Transmitted via **bacterial conjugation** (*independent* of chromosomal replication)
  - Ability for rapid spread of multiple resistance genes to multiple bacterial species
  - Example: evolution of most MDROs with resistance to multiple beta-lactams as well as some other antibiotic classes

Mechanisms of antibiotic resistance

- Enzymatic deactivation of agent outside cell or altered bacterial metabolism
  - Extracellular deactivation: beta-lactamases - penicillins, cephalosporins, carbapenems
  - Intracellular metabolic alteration: sulfa drugs
- Reduced penetration into the bacterial cell or persistence at “target” site
  - Reduced penetration (porin channels): beta-lactams, AGs, quinolones, chloramphenicol
  - Reduced intracellular persistence (efflux pumps): macrolides, TCNs, beta-lactams
- Alteration of specific antibiotic bacterial targets
  - Cell wall penicillin-binding protein alteration: methicillin-resistant Staph
  - Cell wall components: glycopeptides
  - Ribosomal targets: clindamycin, macrolides, tetracyclines
  - DNA gyrase: quinolones

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Beta-lactams

- Penicillins
  - Natural penicillins: pen G, pen VK, benzathine pen [Bicillin], procaine pen
  - Semi-synthetic (expanded-spectrum) penicillins:
    - Amino-penicillins: Ampicillin
    - Ureido-penicillins: Piperacillin
  - Penicillinase-R penicillins*:* oxacillin, methicillin, nafcillin
- Cephalosporins
  - 1st generation: cephalothin, cefazolin, cephalexin
  - 2nd generation: cefuroxime, cefoxitin*, cefotetan* [*cephamycin class]
  - 3rd generation: cefotaxime, ceftriaxone, ceftazidime
  - 4th generation: cefepime
  - "5th generation": ceftaroline
- Carbapenems: imipenem, meropenem, ertapenem
- Monobactam: aztreonam
- Beta-lactam/beta-lactamase inhibitors: amp/sulbactam, pip/tazo, caz/avi, etc.

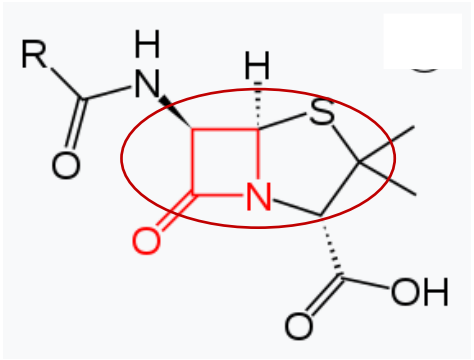
Structure and mechanism of action/resistance

- Structure

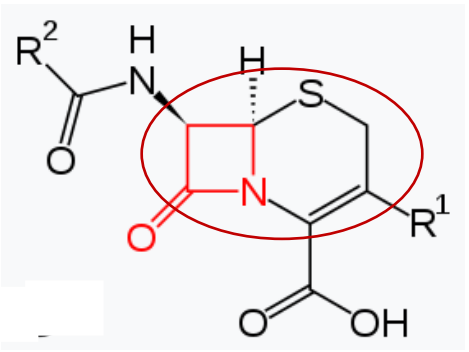
beta-lactam ring

Penam/cepham nucleus

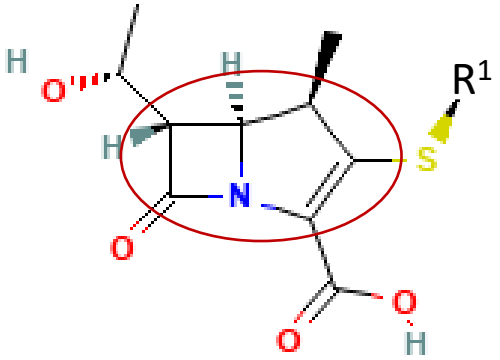
R, R_1, R_2 = side chains



PENICILLINS



CEPHALOSPORINS



CARBAPENEMS

- Mechanism of action/resistance
  - An **active** *beta*-lactam agent ← *inactivating beta-lactamase enzymes*
  - Enters the bacterial cell via **porin channels,** ← *porin channel mutations*
  - **Remains** there long enough to **bind** to cell wall penicillin-binding protein (**PBP**), ← *efflux pumps, PBP mutations*
  - Interferes with ongoing bacterial cell wall synthesis resulting in bacterial death

Spectrum of activity

*Antibiotic effectiveness dependent on development of resistance mutations; **local antibiogram** can help assessment of likely empiric therapy success but only culture/sensitivity result provides definitive answer

- Penicillins
  - Natural penicillins: **Strep spp, Listeria, Clostridia**; most *Staph aureus* now resistant
  - Semi-synthetic (expanded-spectrum) penicillins:
    - Amino-penicillins: Ampicillin above plus ?* **H. flu, Neisseria spp, Salmonella, E.coli, Proteus**
    - Ureido-penicillins: Piperacillin: above plus ?* **Enterobacter, Pseudomonas**
  - Penicillinase-R penicillins: Oxacillin, methicillin, nafcillin ***Staph aureus***
- Cephalosporins
  - 1st generation: cephalothin, cefazolin, cephalexin **Gram(+) +++ Gram(-) +**
  - 2nd generation: cefuroxime, cefoxitin, cefotetan **Gram(+) ++ Gram(-) ++**
  - 3rd generation: cefotaxime, ceftriaxone, ceftazidime* **Gram(+) + Gram(-) +++**
  - "4th generation": cefepime* [spectrum essentially the same as ceftazidime]
  - "5th generation": ceftaroline added **MRSA** activity **Gram(-) ++**
- Carbapenems: imipenem*, meropenem*, ertapenem added **MDRO** activity [ESBL]
- Monobactam: aztreonam* **Gram(-) activity only**

*Non-MDRO Pseudomonas activity

Clinical indications

Reliably good coverage by MOST *beta*-lactam agents
Potential coverage by SOME *beta*-lactam agents
NO potential coverage by MOST lactam agents

- Beta-lactams are the most widely utilized of antibiotics (all classes)
- Empiric (per known clinical syndrome etiology +/- current antibiogram)
  - Skin and soft tissue infections: Staph aureus[#] (including MRSA*), strep[#], ?GNRs
  - Respiratory infections: Pneumococcus[#], H. flu, GNRs (Kleb, etc.), atypicals, viruses
  - Urinary tract infections: E. coli and other GNRs, enterococcus**[#]
  - Abdominal infections: GNRs, anaerobes, enterococcus**[#]/other strep[#]
  - Neurologic infections: Meningococcus, H. flu, pneumococcus*, Listeria**[#]
  - Sepsis: GNRs, Staph aureus[#]/MRSA*, enterococcus**[#]/other strep[#], yeast
- Targeted (per specific cultured pathogen +/- sensitivity results)
  - Choose an effective tolerable agent with the narrowest spectrum/best safety profile
  - Consider: allergy history, patient comorbidities, and potential toxicity of other meds

[#]*NO* Gram(+)s covered by aztreonam

*MRSA *ONLY* covered by ceftaroline

**Some Gram(+)s *NOT* covered by cephalosporins

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
***Beta*-lactam agents**	✔	✔	✔	✔	✔	✔	✔	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✔			✔		✔		VRE (VanA, VanB)
Quinolones		✔	✔	✔			✔	DNA gyrase (gyr)
Aminoglycosides						✔	✔	
Tetracyclines	✔	✔				✔	✔	
Macrolides		✔					✔	Efflux pump
Sulfonamides	✔		✔	✔			✔	
Other antibacterial agents*	✔	✔		✔	✔	✔	✔	
Antifungal agents	✔	✔	✔		✔		✔	
Antiviral agents	✔	✔			✔		✔	
Anti-parasitic agents				✔	✔		✔	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
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Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
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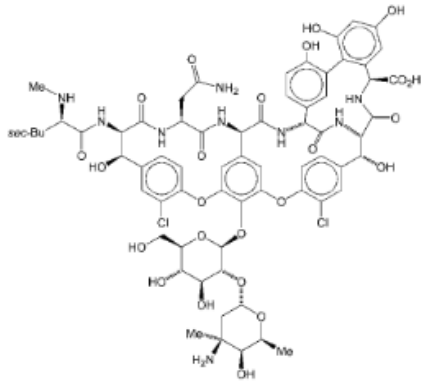
Glycopeptides

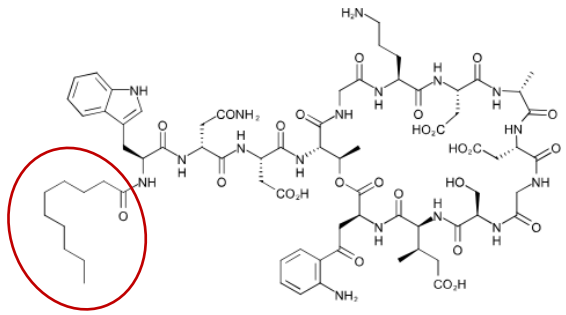
Structure and mechanism of action/resistance

- Structure



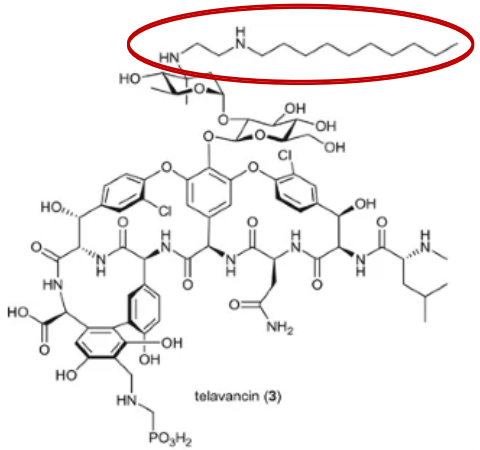
VANCOMYCIN

GLYCOPEPTIDE

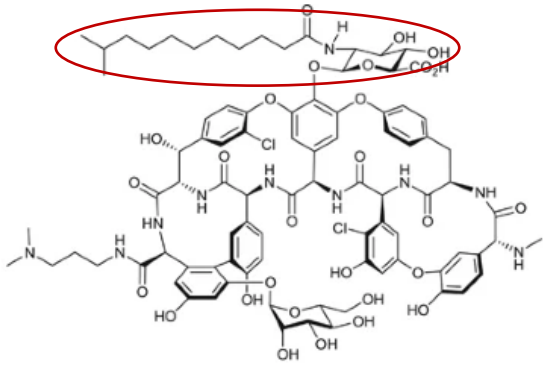


DAPTOMYCIN

LIPO-PEPTIDE



TELAVANCIN



DALBAVANCIN

LIPO-GLYCOPEPTIDES

- Mechanism of action/resistance

Poor vancomycin binding to mutated VRE cell wall precursors

  - Inhibits peptidoglycan synthesis in Gram(+) bacterial wall formation
  - Interferes with ongoing bacterial cell wall synthesis resulting in bacterial death
  - Lipo- and lipo-glyco-peptides can also disrupt the bacterial cell *membrane*

Spectrum of activity

- Vancomycin: **Gram(+) bacteria** excluding VRE and VISA/VRSA
- Daptomycin: **Gram(+) bacteria** including VRE and VISA/VRSA
- Lipoglycopeptides
  - Televancin: **Gram(+) bacteria** including VISA and VanB VRE but not VRSA or VanA VRE
  - Dalbavancin: **Gram(+) bacteria** including VISA and vanB VRE but not VRSA or VanA VRE
  - Oritavancin: **Gram(+) bacteria** including VRE and VISA/VRSA

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Glycopeptides	✓			✓		✓		VRE (VanA, VanB)
Quinolones		✓	✓	✓			✓	DNA gyrase (gyr)
Aminoglycosides						✓	✓	
Tetracyclines	✓	✓				✓	✓	
Macrolides		✓					✓	Efflux pump
Sulfonamides	✓		✓	✓			✓	
Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓		✓		✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

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Quinolones

Structure and mechanism of action/resistance

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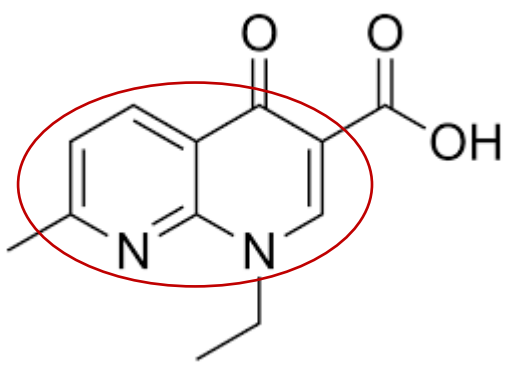
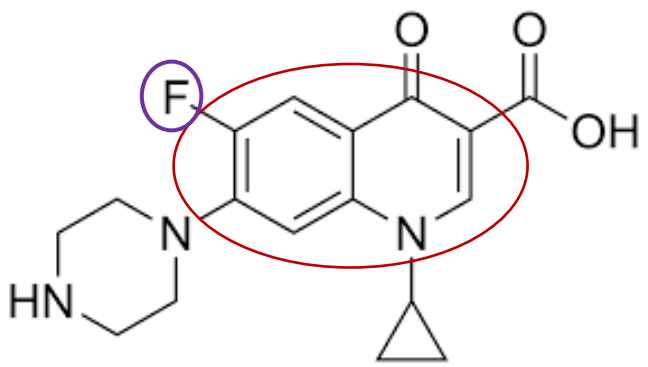
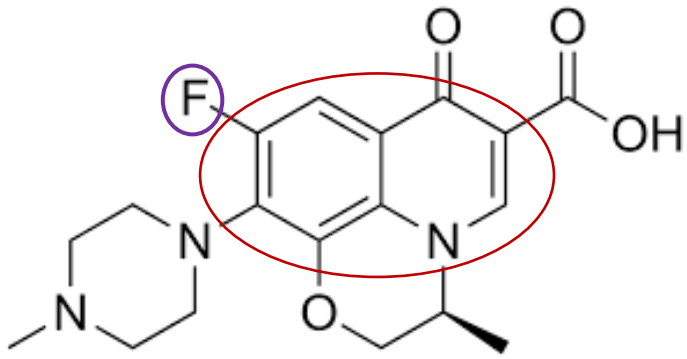


NALIDIXIC ACID



CIPROFLOXACIN



LEVOFLOXACIN

FLUORO-QUINOLONES

- Mechanism of action/resistance
  - A quinolone agent enters the bacterial cell via **porin channels,** ← *porin channel mutations*
  - Binds to bacterial DNA gyrase and inactiviates it, ← *DNA gyrase mutations reduce binding affinity*
  - Thereby interfering with with ongoing bacterial replication

Spectrum of activity

*Antibiotic effectiveness dependent on development of resistance mutations; **local antibiogram** can help assessment of likely empiric therapy success but only culture/sensitivity result provides definitive answer

- Nalidixic acid: **Gram(-) bacteria +** [not Gram(+)s, Pseudomonas, anaerobes]

- Fluroquinolones: **Gram(-) bacteria +++** [including some Pseudomonas]
  Gram(+) bacteria +++ [including enterococcus and MRSA]
  - Ciprofloxacin
  - Levofloxacin

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Quinolones		✓	✓	✓			✓	**DNA gyrase (gyr)**
Aminoglycosides						✓	✓	
Tetracyclines	✓	✓				✓	✓	
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Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓		✓		✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

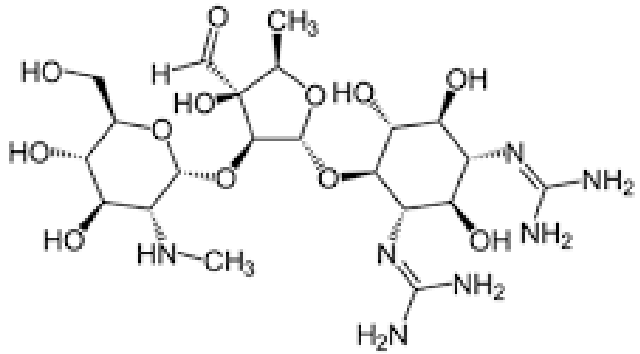
Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	**Tendonopathy**	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

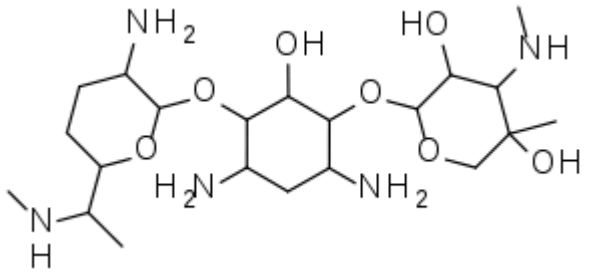
Aminoglycosides

Structure and mechanism of action/resistance

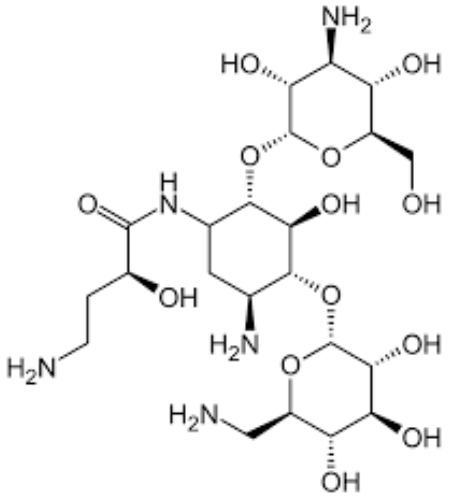
- Structure



STREPTOMYCIN



GENTAMICIN



AMIKACIN

- Mechanism of action/resistance
  - An aminoglycoside avoids extracellular inactivation,
  - Transverses the bacterial cell membrane via active transport,
  - Binds to bacterial ribosome and disrupts protein synthesis causing cell death

Extracellular inactivation from AG-modifying enzymes or purulent fluid

decreased cellular uptake due to mutation, low pH, or hypoxia

modification of ribosomal binding target

Spectrum of activity

*Antibiotic effectiveness dependent on development of resistance mutations; **local antibiogram** can help assessment of likely empiric therapy success but only culture/sensitivity result provides definitive answer

Basic activity shared by most agents

- *Aerobic* **Gram(-) bacteria** including Pseudomonas, Acinetobacter
- Some Neisseria spp
- **Gram(+) bacteria** [in *synergistic* role with other abx vs strep spp., Staph]
- Some mycobacteria spp. (TB and NTM)

Ineffective against:

- Stenotrophomonas, Burkholderia, anaerobic bacteria

Enhanced spectrum with newer agent (Plazomicin)

- ESBL
- CRE (OXA-A type)

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✓	✓	✓	✓	✓	✓	✓	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✓			✓		✓		VRE (VanA, VanB)
Quinolones		✓	✓	✓			✓	DNA gyrase (gyr)
Aminoglycosides		✓	✓	✓		✓	✓	**AG-modifying enzymes, ↓uptake, modified ribosomal target**
Tetracyclines	✓	✓				✓	✓	
Macrolides		✓					✓	Efflux pump
Sulfonamides	✓		✓	✓			✓	
Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓		✓		✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

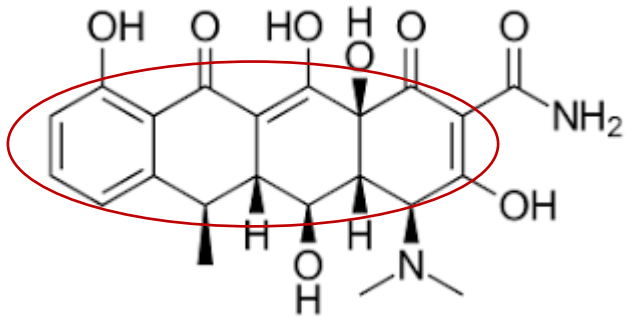
Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		**Ototoxicity**	**Low**	**Low**
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

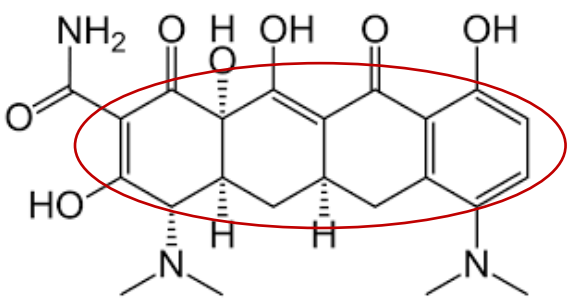
Tetracyclines

Structure and mechanism of action/resistance

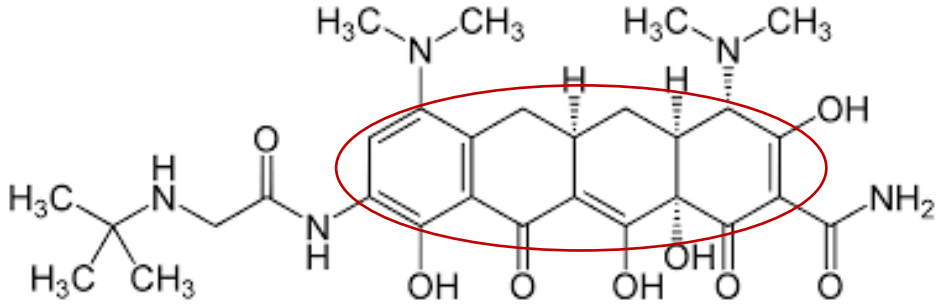
- Structure



DOXYCYCLINE



MINOCYCLINE



TIGECYCLINE

GLYCYLCYCLINE

Not affected by ribosomal protection proteins or many efflux pumps

- Mechanism of action/resistance
  - A tetracycline agent enters the bacterial cell, ← *barrier to influx*
  - Remains intracellular to allow binding to bacterial ribosome,
  - Resulting in interruption of protein synthesis and cell death

30s ribosomal protection protein interference with abx binding, efflux pumps

Spectrum of activity

- Doxycycline/minocycline:
  - Gram(+) [including many MRSA]
  - Gram(-) [both aerobic and anaerobic]
  - Atypical bacteria (Mycoplasma, Chlamydia, Legionella
  - Mycobacteria
  - Rickettsia
  - Spirochetes
- Tigecycline: above + Acinetobacter, VRE, Stenotrophomonas
- Newer agents:
  - Eravacycline: above + Acinetobacter, MDROs (ESBL, KPC, MRSA, VRE)
  - Omadacycline: above + Acinetobacter, Stenotrophomonas, MDROs (ESBL)

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✔	✔	✔	✔	✔	✔	✔	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✔			✔		✔		VRE (VanA, VanB)
Quinolones		✔	✔	✔			✔	DNA gyrase (gyr)
Aminoglycosides						✔	✔	
Tetracyclines	✔	✔		✔		✔	✔	**Resistance mutations rare**
Macrolides		✔					✔	Efflux pump
Sulfonamides	✔		✔	✔			✔	
Other antibacterial agents*	✔	✔		✔	✔	✔	✔	
Antifungal agents	✔	✔	✔		✔		✔	
Antiviral agents	✔	✔			✔		✔	
Anti-parasitic agents				✔	✔		✔	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

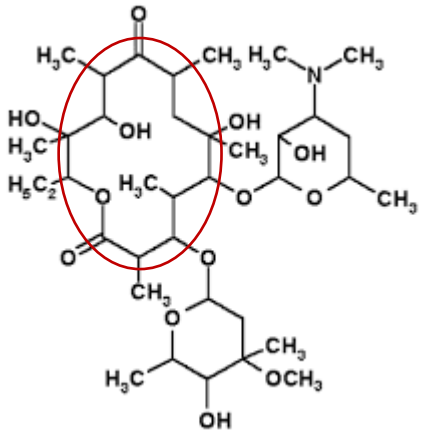
Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		**Hepatic, photosensitivity**	**Low**	**Low to moderate**
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

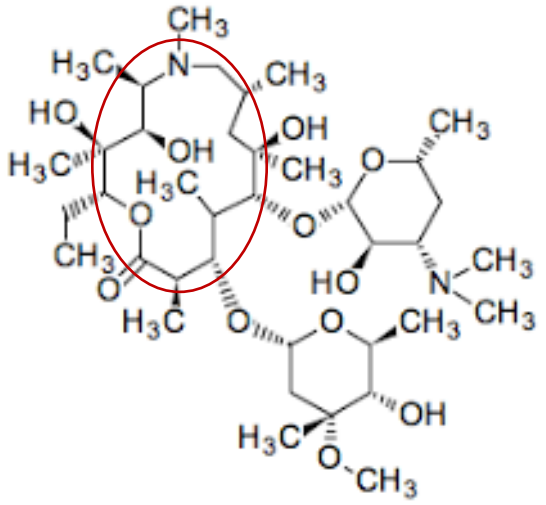
Macrolides

Structure and mechanism of action/resistance

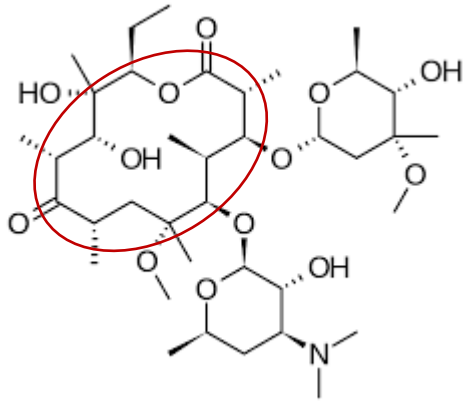
- Structure



ERYTHROMYCIN



AZITHROMYCIN



CLARITHROMYCIN

- Mechanism of action/resistance
  - A tetracycline enters the bacterial cell,
  - Remans intracellular to allow binding to the bacterial ribosome,
  - Resulting in interruption of protein synthesis and cell death

ribosomal protection protein interference with 50s abx binding site, efflux pumps

Spectrum of activity

- Erythromycin
  - **Gram(+) bacteria**: MSSA, strep spp. [except enterococcus], Corynebacteria, Listeria
  - Atypical pathogens: Mycoplasma, Chlamydia, Legionella

- Azithromycin/clarithromycin
  - Shares above spectrum (more active than erythromycin against many pathogens)
  - Non-tuberculous mycobacteria (NTM)
  - Sexually-transmitted diseases (STDs): syphilis, chlamydia, gonorrhea

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✔	✔	✔	✔	✔	✔	✔	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✔			✔		✔		VRE (VanA, VanB)
Quinolones		✔	✔	✔			✔	DNA gyrase (gyr)
Aminoglycosides						✔	✔	
Tetracyclines	✔	✔				✔	✔	
Macrolides		✔					✔	**Efflux pump (mef), altered binding site (ermA,B,C)**
Sulfonamides	✔		✔	✔			✔	
Other antibacterial agents*	✔	✔		✔	✔	✔	✔	
Antifungal agents	✔	✔	✔		✔		✔	
Antiviral agents	✔	✔			✔		✔	
Anti-parasitic agents				✔	✔		✔	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

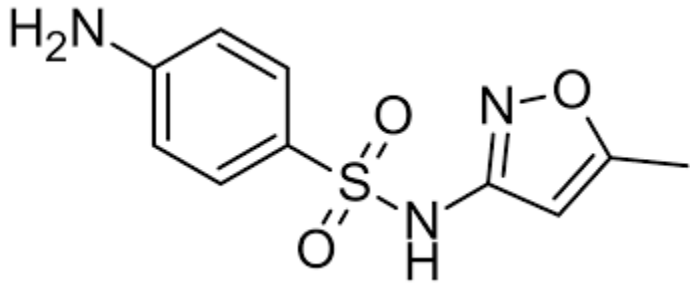
Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			**Rare ototoxicity**	**Low-Moderate**	**Low to moderate**
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

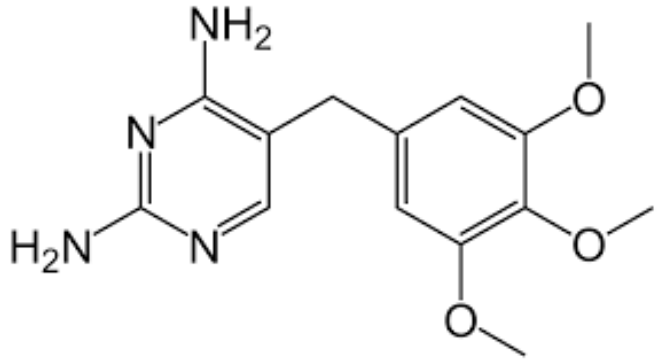
Sulfa drugs

Structure and mechanism of action/resistance

- Structure



SULFAMETHOXAZOLE



TRIMETHOPRIM

- Mechanism of action/resistance
  - Sulfa drugs enter cell and inhibit bacterial nucleic acid synthesis,
  - [Addition of trimethoprim inhibits an *additional* step in the metabolic sequence,]
  - Resulting in failure of bacterial growth

  [*The targeted metabolic process is unique to bacteria and not shared by humans*]

Mutations resulting in increased substrate levels or lower affinity for the antibiotic substrate

Spectrum of activity

*Antibiotic effectiveness dependent on development of resistance mutations; **local antibiogram** can help assessment of likely empiric therapy success but only culture/sensitivity result provides definitive answer

All sulfa drugs have similar spectrum of activity [list below is for SMX-TMP]

- **Gram(+) bacteria**: MSSA and MRSA, beta-hemolytic strep, pneumococcus
- **Gram(-) bacteria**: Aerobic pathogens including Stenotrophomonas
- Other pathogens: Pneumocystis, Mycobacteria (NTM), Listeria

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✓	✓	✓	✓	✓	✓	✓	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✓			✓		✓		VRE (VanA, VanB)
Quinolones		✓	✓	✓			✓	DNA gyrase (gyr)
Aminoglycosides						✓	✓	
Tetracyclines	✓	✓				✓	✓	
Macrolides		✓					✓	**Efflux pump**
Sulfonamides	✓		✓	✓			✓	
Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓		✓		✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			**Hepatic, hematologic**	**Low- Moderate**	**Moderate**
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

Other antibacterial agents

Other antibacterial agents

ROUTINELY-UTILIZED

- Clindamycin
- Fidaxomycin
- Linezolid
- Metronidazole
- TB-specific agents
  - Isoniazid (INH)
  - Rifampin
  - Ethambutol
  - Pyrazinamide (PZA)

SPECIAL SCENARIO RESPONSE

- Cefiderocol (Fetroja)
- *Ceftalozane-Tazobactam (Zerbaxa)*
- *Ceftazidime-Avibactam (Avycaz)*
- Colistin
- *Meropenem-Vaborbactam (Vabomere)*

[italicized *beta*-lactam agents previously mentioned]

Other antibacterial agents

AGENT	CLASS	TARGET/SPECTRUM	SIDE EFFECTS/TOXICITY
Clindamycin	Lincosamide	50s ribosome/anaerobes, staph, strep	Diarrhea/CDI, rash
Fidaxomicin	Macrolide	RNA polymerase/*C. difficile*	GI upset, rash
Linezolid	Oxazolidinone	50s ribosome/GPC including MRSA and VRE	Neuropathy, GI upset, low platelets
Metronidazole	Nitroimidazole	DNA-toxic metabolite/anaerobes, protozoa	GI upset, neuropathy
Rifampin	Rifamycin	RNA polymerase/TB and NTM, staph	Orange urine/tears, “flu-like” sx
Cefiderocol	Beta-lactam	Cell wall/MDR GNRs including CRE strains	Similar to other beta-lactams
Colistin	Polymyxin	Cell membrane/MDR GNRs	Renal

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✓	✓	✓	✓	✓	✓	✓	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✓			✓		✓		VRE (VanA, VanB)
Quinolones		✓	✓	✓			✓	DNA gyrase (gyr)
Aminoglycosides						✓	✓	
Tetracyclines	✓	✓				✓	✓	
Macrolides		✓					✓	**Efflux pump**
Sulfonamides	✓		✓	✓			✓	
Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓		✓		✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔	Rare cytopenias, rare AIN	Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, "red man" rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					**Varies by agent**	**Depends on agent**	**Depends on agent**
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

Antifungal agents

Mechanism of action and clinical indications

- Polyenes – *alter membrane permeability*
  - Nystatin: candida spp.
  - Amphotericin: cocci, crypto, histo, blasto, candida spp., aspergillus, mucor*
- Azoles – *alter membrane permeability*
  - Fluconazole: candida spp., crypto, cocci
  - Voriconazole: aspergillus, candida spp.
  - Itraconazole: aspergillus, blasto, histo
- Echinocandins – *interfere with cell wall synthesis*
  - Micafungin: candida spp.
- Antimetabolites – *inhibit nucleic acid synthesis*
  - Flucytosine: candida spp.; crypto

*Treatment can also involve some advanced azole agents:
- Posacomazole
- Isavuconazole

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✓	✓	✓	✓	✓	✓	✓	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✓			✓		✓		VRE (VanA, VanB)
Quinolones		✓	✓	✓			✓	DNA gyrase (gyr)
Aminoglycosides						✓	✓	
Tetracyclines	✓	✓				✓	✓	
Macrolides		✓					✓	**Efflux pump**
Sulfonamides	✓		✓	✓			✓	
Other antibacterial agents*	✓	✓		✓	✓	✓	✓	
Antifungal agents	✓	✓	✓	✓	✓	✓	✓	
Antiviral agents	✓	✓			✓		✓	
Anti-parasitic agents				✓	✓		✓	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

Antiviral and anti-parasitic agents

Antiviral and anti-parasitic agents

ANTIVIRAL

- Influenza
- COVID
- Herpes simplex
- Varicella zoster
- Cytomegalovirus (CMV)
- HIV
- Hepatitis B and hepatitis C

ANTI-PARASITIC

- Giardia and other GI parasites
- Scabies
- Amebiasis
- Malaria
- Neurocysticercosis
- Disseminated strongyloides
- Chagas disease

Summary of antimicrobial class characteristics

Antimicrobial Class	1st agent discovered	General *bacterial* activity spectrum				Relative CDI risk	Allergy issues
		Gram(+)	Gram(-)	AnO2	Other*		
Beta-lactam agents	1928					Depends on agent	Moderate to high
Glycopeptides	1958		X		X	Low	Low to moderate
Quinolones	1962			X		High	Low to moderate
Aminoglycosides	1967	X		X		Low	Low
Tetracyclines	1945					Low	Low to moderate
Macrolides	1952			X		Low-Moderate	Low to moderate
Sulfonamides	1932			X		Low- Moderate	Moderate
Other antibacterial agents	1953					Depends on agent	Depends on agent
Antifungal agents	1949	X	X	X		n/a	Low
Antiviral agents	1963	X	X	X		n/a	Low
Anti-parasitic agents	1960	X	X	X		Low	Depends on agent

*Other: Mycobacteria, Mycoplasma, Nocardia, Rickettsiae, Spirochetes; fungi, viruses, parasites

Summary of antimicrobial class indications

Antimicrobial Class	SSTI	Resp	GU	GI/ Abd	Neuro	Sepsis	Other[#]	Common resistance mutations (genes) and Comments
Beta-lactam agents	✔	✔	✔	✔	✔	✔	✔	MRSA (mecA/C), ESBL (CTX-M), CRE (OXA,KPC,MBL)
Glycopeptides	✔			✔		✔		VRE (VanA, VanB)
Quinolones		✔	✔	✔			✔	DNA gyrase (gyr)
Aminoglycosides						✔	✔	
Tetracyclines	✔	✔				✔	✔	
Macrolides		✔					✔	Efflux pump
Sulfonamides	✔		✔	✔			✔	
Other antibacterial agents*	✔	✔		✔	✔	✔	✔	
Antifungal agents	✔	✔	✔	✔	✔	✔	✔	
Antiviral agents	✔	✔			✔		✔	
Anti-parasitic agents				✔	✔		✔	

*Anti-TB agents, clindamycin, colistin, linezolid, metronidazole

[#]for example: other sites; Mycobacterial, Rickettsial, or STD infection

Summary of antimicrobial class side effects

Antimicrobial Class	Skin	GI	Renal	Neuro	Other side effects	CDI risk	Allergy frequency
Beta-lactam agents	✔	✔		✔		Depends on agent	Moderate to high
Glycopeptides			✔		Ototoxicity, “red man” rash	Low	Low to moderate
Quinolones		✔		✔	Tendonopathy	High	Low to moderate
Aminoglycosides			✔		Ototoxicity	Low	Low
Tetracyclines		✔	✔		Hepatic, photosensitivity	Low	Low to moderate
Macrolides		✔			Rare ototoxicity	Low-Moderate	Low to moderate
Sulfonamides	✔	✔			Hepatic, hematologic	Low- Moderate	Moderate
Other antibacterial agents					Varies by agent	Depends on agent	Depends on agent
Antifungal agents					Varies by agent	n/a	Low
Antiviral agents					Varies by agent	n/a	Low
Anti-parasitic agents					Varies by agent	Low	Depends on agent

Game plan

- Introduction/5-on-5 analogy?
- Review of antibiotics and their evolution
  - Role of resistance in abx development and utilization
  - How resistance occurs: plasmid vs chromosomal
  - Pharma and the drug discovery/approval process
- Review of specific antimicrobial classes and select agents
- Current terrain: MDROs, restricted abx, order sets, empiric use/de-escalation
- AS teamwork: shared goals/different roles (pharmacy, providers, RNs, lab, IP)
- Examples
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Current terrain: "pre-game" assessment

- Look to your "scouting report" (current antibiogram including MDROs)
  - Contains data on relative *number* of pathogens, not just sensitivities
  - Your "Starting 5" drugs (empiric abx choices) should match up against the most commonly encountered ("Starting 5") bugs
  - If this is not the case, consider *adjusting your rotation* ("starters" vs "subs")
    - An opposing MDRO may warrant starting a Restricted Antibiotic
    - Sensitivity data/trends can help you prepare for *current* MDRO likelihood
- Do you have court advantage? [favorable/unfavorable patient factors]
  - Home court: healthy young patient with no abx allergies, no or few comorbidities
  - Hostile court: unhealthy older patient with abx allergies, significant comorbidities
- Any players on the DL (Disability List)?: Abx shortages, formulary restrictions
- Will you plan out the initial sequence of plays?: Order sets, clinical pathways

Current terrain: making "in-game" decisions

- Empiric choices – your "starters"
  - Utilize what data is available to guide *initial* choice(s)
  - Minimize *treatment* coverage gaps during early hospital course/observe for response
  - Accept risk of an *initially* broad/potent empiric antibiotic regimen (cost/benefit)
- Targeted choices – *informed* substitutions according to the "flow of the game"
  - More data available each day
  - As patient improves/?responds, can afford some potential gaps in narrowed treatment
  - Seek to limit risk of extended *broad* antibiotic use (choose the safest effective agents)
- Antibiotic de-escalation or discontinuation – optimal "clock management"
  - Antibiotic "time-out" at 48-72 hours to reassess decisions with benefit of more data
  - ?Narrow (de-escalate) or discontinue: *OK to consider **stopping** if cultures negative*
  - Observe recommended treatment durations: growing evidence for shorter rx courses

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Different roles/shared goal

- Different roles:
  - Pharmacy: manage abx formulary, monitor usage for optimization opportunities
  - Providers: order abx, determine targeted abx changes and treatment duration
  - Bedside RNs: monitor for side effects, assess patient response/tolerance to rx
  - Microbiology lab: provide preliminary/final C&S results, furnish antibiogram
  - IP: monitor/report MDRO infections, provide diagnostic stewardship education
- Shared goal: WIN
  - Avoid a “Bugs defeat Drugs” headline on the next morning’s sports page
  - Work together to maximize the chance of successfully treating each infection while minimizing the risk of negative consequences to the patient (side effects, prolonged stay) and the ministry (increased antibiotic resistance, excessive costs)

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- Scenario: 40-yo female with lower extremity non-purulent cellulitis worsening over past week in the context of chronic edema; low-grade fever, mild WBC elevation, no DM; remote history of mild ampicillin rash

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- Suspected pathogens/empiric antibiotic choice(s):
  - Beta-hemolytic strep – penicillin, ampicillin, cefazolin, clindamycin
  - Staph aureus – oxacillin, cefazolin, clindamycin
  - MRSA – vancomycin, TCN, Bactrim, clindamycin, ceftaroline
  - GNRs/anaerobes – amp/sulbactam, pip/tazo, metronidazole

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- Subsequent data/treatment alteration?
  - Nares MRSA screen negative
  - WBC improving, CRP declining, cellulitis improving; no sign of allergic reaction
  - Consider: **de-escalation** to oral agent (cephalexin, oral clindamycin)

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  - Atypical pathogens (Mycoplasma, Legionella) – azithromycin, doxycycline
  - Viruses – influenza (oseltamivir), COVID (Paxlovid, Remdesivir)
  - Nosocomial pathogens – MRSA, GNRs (incl. MDROs) – vanco, cefepime, meropenem

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- Subsequent data/treatment alteration?:
  - Respiratory antigen panel negative for flu A, flu B, COVID; nares MRSA negative
  - Oxygenation, WBC elevation, PCT worsening; sputum cx pending/GNRs on smear
  - Consider: treatment **escalation** to include nosocomial GNRs/MDROs

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  - Strep species (including enterococcus) – vancomycin, beta-lactams, clindamycin
  - Anaerobes – metronidazole, clindamycin, pip/tazo, meropenem
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- Subsequent data/treatment alteration:
  - BC non-ESBL Proteus, IR-placed abscess drain Proteus & non-VRE strep; nares MRSA(-)
  - Elevated WBC, PCT, temps persisting; repeat CT suggests inadequate abscess drainage
  - Consider: **continuing current regimen** pending better source control (repeat IR drain)

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