Core Concepts: Antibacterial Drugs II Gram Positive Organisms

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- Editor: ID Clinics of North America, Sanford Guide

Overview of Antibacterial Mechanisms
To Orient You: Little is Testable

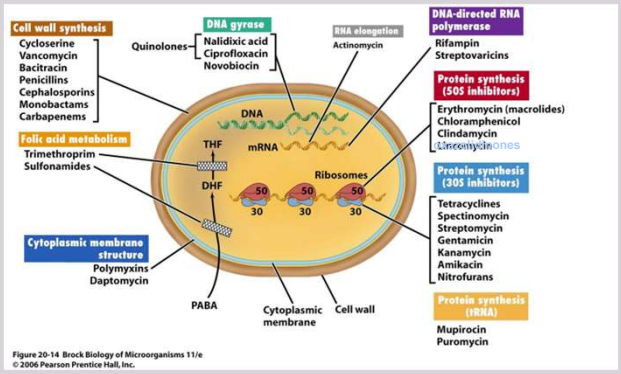

Figure 20-14 Brock Biology of Microorganisms 11/e
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SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Cell Wall Active Agents

- Penicillins
- Cephalosporins
- Carbapenems
- Vancomycin
- Daptomycin
- Polymyxins
- Aztreonam

β-lactam Spectrum

- Penicillins
- Semi-synthetic penicillins
- 1st gen cephalosporins
- 2nd gen cephalosporins
- 3rd gen cephalosporins
- 4th gen cephalosporins
- Carbapenems
- Monobactams

Gram-positive

Gram-negative

β-lactam Antibiotics Share Mechanism of Action

- Why are there different spectrum of activity for penicillins, cephalosporins, carbapenems?
  - Broad and narrow susceptibility to beta-lactamases
  - Different penicillin binding proteins
  - Selective efflux pumps
  - Ability to reach target site

β-lactam Adverse Effects

- Anaphylaxis / allergy
  - See lecture by Dr. Sandy Nelson
- Seizures
  - Imipenem, cefepime
- Myelosuppression, leukopenia, hemolytic anemia
- Hypersensitivity hepatitis: e.g., Oxacillin
- Biliary stasis/sludging
  - Ceftriaxone
- Renal
  - Interstitial nephritis

Question #1

What is the only cephalosporin active against MRSA?

A. Cefpodoxime
B. Cefepime
C. Ceftobiprole
D. Cefixime
E. Cefoxitin

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Cephalosporins

- Bactericidal
  - Inhibit bacterial cell wall synthesis
- Time dependent killing
- Resistance mostly due to susceptibility to β-lactamases
- Fewer allergic reactions than PCN
- CSF penetration with third generation
- Most renally excreted

Key Points About Cephalosporin Activity

- Enterococci
  - None are active
- MRSA
  - Only ceftaroline and ceftobiprole active
- Anaerobic activity
  - Only Cephamycins active
    - (e.g., cefoxitin, cefotetan)
    - Now high levels of resistance

Ceftaroline Fosamil – a Prodrug (IV and IM, Not Oral)

- Activity
  - Gram-positive including MRSA and MDR S. pneumoniae
    - Some activity vs E. faecalis; not E. faecium
  - Limited activity vs. anaerobes
    - Active vs Cutibacterium (formerly Propionobacterim) acnes, Actinomyces spp.

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156

Ceftaroline Fosamil – a Prodrug (IV and IM, Not Oral)

- Activity
  - Active vs Gram-negative pathogens
    - *E. coli, Klebsiella spp., H. influenzae* (incl B-lactamase positive), *M. catarrhalis*
  - **Not Pseudomonas or ESBL+ GNB**
  - **Similar spectrum to ceftriaxone**
- Bactericidal, time dependent killing

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156

Ceftobiprole

- Advanced spectrum IV cephalosporin
- Broad spectrum (similar to ceftaroline)
  - Active vs G+ incl PRSP, MRSA, anaerobes
  - Some activity vs E. faecalis; not E. faecium
  - Active vs Enterobacteriaceae
  - Not active vs CRE, P aeruginosa

Overcash et al. CID 2021: 73: e1507; Awad SS et al. Clin Infect Dis. 2014;59(1):51–61
Holland et al. N Engl J Med 2023: 389(15):1390

Ceftobiprole

- FDA approved:
  - ABSSSI, CABP, *S. aureus* bloodstream infection/Right-sided endocarditis
- Not FDA approved for VABP
  - EU approved HAP not VAP
  - Early HABP studies failed; low ceftobiprole levels found in young ICU patients
- Dosing
  - ABSSSI and CABP:
    - 667 mg IV q 8h x 5-14 days
  - S. aureus bloodstream infection:
    - 667mg IV q 6h day 1-8 then 667 mg IV q 8h day 9+ (thru 42)

Overcash et al. CID 2021: 73: e1507; Awad SS et al. Clin Infect Dis. 2014;59(1):51–61
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Vancomycin

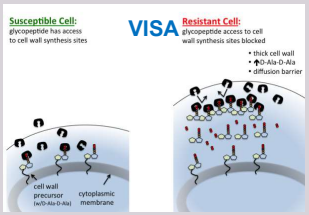
- Bactericidal (slowly)
  - Inhibits bacterial cell wall synthesis
- Active against:
  - Gram Positive Aerobes
    - Streptococcus
    - Staphyloccus
    - Enterococcus
  - Gram Positive Anaerobes
    - Clostridia
    - Propionibacteria
    - Peptostreptococci
    - Actinomyces

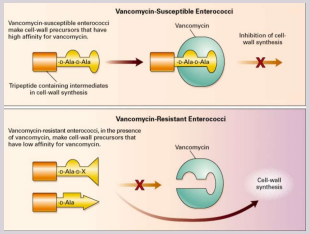
Vancomycin Resistance

- VISA
  - Thick walls, generous binding sites…
- Vancomycin resistance
  - Not in Streptococcus
  - RARE in Staphylococcus
  - Common in Enterococcus
    - Rare in *E. faecalis* (4% in 2014)
    - Common in *E. faecium* (71% in 2014)
    - Mechanism
      - Change in vancomycin binding site on peptidoglycan

Vancomycin Resistance

- VISA thickened cell wall + xs vancomycin binding sites (D-Ala-D-Ala); result: vanco trapping with reduced cellular targets
- VRE – replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini – result: decreased **vancomycin** binding affinity --- high level resistance: MIC increase x 1000





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Murray NEJM 2000

Vancomycin for MRSA Bloodstream Infection

- Controversy re: optimal therapy – see Dr. Chambers lecture
- Vancomycin trough only monitoring no longer recommended
  - Target AUC/MICBMD ratio of 400 to 600
    - (Assume vancomycin MIC_{BMD} = 1 mg/L)
- Loading dose for seriously ill adults
  - 20–35 mg/kg can be considered
  - Pediatric doses higher
    - 60-80 mg/kg/day divided q 6-8 hours

- **Dosing Calculator helps!**

https://www.idsociety.org/practice-guideline/vancomycin/

Vancomycin ADRs / Interactions

Adverse Drug Reactions

- Nephrotoxicity
  - Duration > 14d
  - Dose > 4g / day
  - Trough > 20
- Ototoxicity
- Histamine Release Syndrome
- DRESS
- Immune thrombocytopenia
- Neutropenia
- IgA bullous dermatitis

Drug Interactions

- Increased nephrotoxicity when given with other nephrotoxins
  - Aminoglycosides
  - NSAIDs
  - Contrast
  - Cyclosporine
  - Tacrolimus
  - Loop Diuretics
  - ACE inhibitors
  - Pip/tazo (pseudo interaction)

Daptomycin (IV)

- Antimicrobial Class: Lipopeptide
- Broad spectrum gram + activity
  - Including MRSA
- Rapidly bactericidal
- Concentration-dependent killing
- Indications
  - cSSSI
  - *S. aureus* bloodstream infection
  - Right-sided endocarditis

Fenton C et al. *Drugs* 2004; 64: 445-55, Tedesco KL, Rybak MJ. *Pharmacother* 2004; 24:41-57, Mangili A et al. *Clin Infect Dis* 2005; 40:1058-60, Fowler VG et al. *New Engl J Med* 2006; 355:653-665

Daptomycin for *S. aureus* Bacteremia and Right IE

- Pneumonia
  - Do not use: surfactant binding inactivates drug
- Monitoring
  - CPK twice weekly
  - Discontinue if myopathy or CPK > 5x ULN
- Toxicity
  - Eosinophilic Pneumonia
    - Rx supportive care and steroids
  - Falsely prolonged Prothrombin Time
  - Muscle inflammation
    - CPK increase, myopathy, myositis
    - Risk factors: renal failure, statins, obesity

Vancomycin and Daptomycin

Drug	Mechanism of Action	Mechanism of Resistance	Spectrum	Adverse Event
Vancomycin	Inhibits cell wall synthesis (not a beta lactam)	Change in cell wall terminus from D-ala-D-ala to D-ala-D-lactate (high level resistance)	Gram positive cocci only including MRSA	• Histamine release syndrome • Kidney toxicity
Daptomycin	Cell membrane depolarization Potassium efflux	• Decreased binding of drug to cell membrane • Altered cell membrane potential	Resistant gram-positive cocci including MRSA and VRE Inactivated by surfactant (not for pneumonia)	• Skeletal muscle toxicity

Oritavancin and Dalbavancin Long-Acting Glycopeptides

- Mechanism of Action
  - Similar to vancomycin
  - Inhibition of cell wall synthesis
- Dosing
  - Oritavancin: IV only: 1 dose (1200 mg over 3hours)
  - Dalbavancin: IV only: 1000mg, then 500mg every 7 days …OR 1500mg x 1
- Approved
  - Skin and Soft Tissue
  - Oritavancin FDA warning against use in osteomyelitis
  - Dalbavancin also used for osteomyelitis, right sided endocarditis
- Toxicity
  - Oritavancin prolongs aPTT (artificially), PT, and activated whole blood clotting time (ACT) for 5 days

Lipo/Glycopeptide Testable Toxicities

- Vancomycin: Nephrotoxicity, Histamine Release
- Daptomycin: CPK elevation, myopathy, rhabdomyolysis; eosinophilic pneumonia
- Telavancin: Nephrotoxicity
- Oritavancin: LFT elevation, false prolongation of aPTT
- Dalbavancin: LFT elevation

Question #2

Which quinolone has activity against MRSA?

A. Ciprofloxacin
B. Moxifloxacin
C. Trovafloxacin
D. Delafloxacin
E. Levofloxacin

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Antibiotics Active Intracellularly

- Fluoroquinolones
- Tetracyclines
- Linezolid
- TMP/SMX
- Pleuromutilins
- Linezolid/Tedizolid

Fluoroquinolone Mechanism of Action and Resistance

- Topoisomerase inhibitors
  - Inhibits DNA gyrase and topoisomerases II and IV
  - Gyrase more for gram negs, topos for gram pos
- Resistance
  - Target site mutations
  - Drug permeability mutations
  - Occurs spontaneously on therapy
  - Susceptible to drug modifying enzymes

Fluoroquinolones
Spectrum of Gram-positive Activity

	Gram-positive	Gram-negative	Anaerobes
Cipro	Poor strep Some MSSA	Best FQ for • Pseudomonas • *E coli*	Some
Levo	Good strep Some MSSA	Best for *Stenotrophomonas spp.*	Some
Moxi	Good strep Good MSSA	**Not effective** • **Don't use for UTI**	**Best**

Drs. Tamma and Gilbert will address Gram-negative activity

Fluoroquinolone Pharmacokinetics

- High oral bioavailability
  - >95% for moxi / levo, 70-80% for cipro
  - Potential low bioavailability when taken with multivalent cations – chelation blocks absorption
- Widely distributed to tissues
  - Lower than serum but therapeutic concentration in CSF, saliva, bone, ascitic fluid and prostate gland
- Elimination
  - Levo / cipro: renal through tubular secretion
  - Moxi: >60% hepatic / biliary unchanged

Fluoroquinolone Adverse Effects

- *C. difficile*
- Arthropathy/cartilage toxicity / tendonitis
  - FDA Warning for rare tendon rupture
    - Increased risk: advanced age, poor renal function, concomitant steroids
- Altered mental status (HA, dizziness, insomnia)
- Dysglycemia-FDA warning especially for older adults and diabetics
  - Hypo- and hyperglycemia
- Aortic aneurysm and aortic dissection-FDA warning
  - Association is controversial
- QTc Prolongation:
  - Moxi > levo ? Cipro
  - Increased risk:
    - Concomitant QTc prolongers, cardiomyopathy, bradycardia, low K+ and Mg++

Delafloxacin

- Broad spectrum fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Broad spectrum including Pseudomonas
- Dosing IV and oral twice daily
- Approved for skin and soft tissue infections

Saravolatz LD and Stein GE. Clin Infect Dis. 2019;68(6):1058–62

Tetracyclines: Major Clinical Uses

- Acne (minocycline)
- Respiratory tract infections
  - Atypical pneumonia
- Sexually Transmitted Diseases
  - Syphilis (*T. pallidum*) – alternative therapy
  - *Chlamydia spp*.
- Tick-Borne Illnesses
  - Lyme disease
  - Anaplasmosis
  - Ehrlichiosis
  - Rocky Mountain Spotted Fever
- Community Acquired MRSA infections

Tetracyclines: Adverse Effects

- Gastrointestinal
  - Nausea
  - Esophageal ulceration
  - Hepatotoxicity
- Skin
  - Photosensitivity
- Children
  - Yellow brown tooth discoloration if age <8 yrs for tetracyclines
  - **Doxycycline therapy OK for ≤21 days in children of all ages**
    - Ref: Redbook 2018 and Am Academy Pediatrics
- Pregnancy
  - Tetracyclines cross the placenta; accumulate in fetal bone/teeth
  - Most tetracyclines contraindicated in pregnancy

Newer Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily No dose adjustment for renal/hepatic impairment	1mg/kg IV q 12h (over 60 minutes) Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

Question #3

What is the major advantage of tedizolid compared to linezolid?

A. Longer half life
B. Better penetration of prostate
C. Better CSF Penetration
D. Wide spectrum of activity against anaerobes
E. More effective in clinical studies for VRE

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Linezolid and Tedizolid
Oxazolidinone Drug Class

- Mechanism
  - Binds 50s ribosome/prevents formation of initiation complex
- Spectrum of activity
  - Gram positive cocci including MRSA and VRE
    - Linezolid resistant *S.aureus* reported
  - Mycobacteria
- Resistance is rare; target change
- Linezolid twice daily; Tedizolid once daily
- FDA approvals for Linezolid:
  - Skin and Soft Tissue, Pneumonia, VRE
  - NOT Bloodstream infection (Black Box Warning)

Shinabarger DL et al. *Antimicrob Agents Chemother* 1997; 41: 2132-36; Swaney Sm et al. *Antimicrob Agents Chemother* 1998; 42: 3251-55; French G. *Int J Clin Pract* 2001; 55: 59-63

Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and irreversible optic neuropathy
  - Rare:
    - Lactic acidosis, **serotonin syndrome (w SSRIs)**
- ↑ mortality in study of intravenous catheter-associated bacteremia

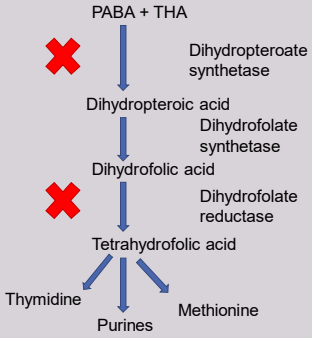
Tsiodras S et al. *Lancet* 2001;358: 207-208; Pillai SK et al. *Clin Infect Dis* 2002; 186: 1603-7; Wilson P et al. *J Antimicrob Chemother* 2003;51:186-88; Medwatch March 16, 2007

Sulfonamides & TMP/SMX

- 1st clinically used antibiotic: sulfanilamide
  - Identified as anti-streptococcal in 1932
  - Initially an industrial dye
  - Changed the face of WWII
- Combined with trimethoprim 1968
- Off-shoot: methotrexate
  - Used for various hematologic, oncologic, and rheumatologic conditions

TMP/SMX Mechanism of Action

- Together inhibit folic acid synthesis
- Sulfamethoxazole
  - Competitively inhibit incorporation of para-amino benzoic acid (PABA) into tetrahydropteroic acid (THA)
    - SMX has higher affinity for THA than PABA does
- Trimethoprim
  - Inhibits dihydrofolate reductase (DFHR)
  - 50,000 to 100,000 times more active against bacterial DFHR than human enzyme



TMP/SMX Resistance Mechanisms

Sulfamethoxazole

- PABA overproduction
  - Caution with OTC PABA supplements
- Structurally mutated dihydropteroate synthetase
- Decreased bacterial cell permeability

Trimethoprim

- Novel plasmid-mediated DFHR
- Altered cell permeability
- Loss of binding capacity
- Overproduction of or alterations in dihydrofolate reductase

TMP-SMX Adverse Effects

- Anaphylaxis
- Skin rashes
- Bone marrow toxicity
- Kernicterus
- Hemolysis (G6PD def)
- Hepatitis

HIGH PLASMA PROTEIN BINDING

- Gastrointestinal effects
- "Nephrotoxicity"
- Fever
- Drug-drug interactions
- Hyperkalemia

COMPETES FOR TUBULAR SECRETION

TMP/SMX Spectrum of Activity: Typical Bugs

- **Gram Positive**
  - Staphylococci: great
  - Streptococci: controversial
  - Enterococcus: not effective
- **Gram Negative**
  - *E. coli*: ok, increasing resistance
  - Enterobacterales: relatively effective
  - Pseudomonas / Acinetobacter: not effective
  - Stenotrophomonas: often drug of choice (2024 IDSA Guidance suggests combination with cefiderocol, minocycline or levofloxacin)

TMP/SMX Spectrum of Activity Odd Bugs

- *Stenotrophomonas maltophila*
- *Listeria monocytogenes*
- *Nocardia*
- *Moraxella catarhallis*
- *Pneumocystis jirovecii*
- *Toxoplasmosis gondii* (but not superior to pyr/sulf)
- *Chlamydia* (but enough resistance that its not used for STDs)
- Atypical *mycobacteria*

Lefamulin

- Pleuromutilin antibiotic with IV and PO formulation
  - Protein synthesis inhibitor
  - Bacteriostatic
- FDA Approved community acquired bacterial pneumonia
  - Non-inferior to moxifloxacin for CABP in two studies
    - **5 days** of po lefamulin vs. 7 days of po moxifloxacin

File CID 2019

Macrolides (Erythro, Clarithro, Azithro)
Protein Synthesis Inhibitor Binds 50s Ribosome

Spectrum:

CABP Pathogens:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Leigonella spp.*
- *C. pneumoniae*
- Streptococcus groups A, C, and G

Strep Pneumo Resistance

- Rising rates in US
  - Don't use macrolides if local rates of resistance > 25%

Macrolide Spectrum

STDs
- *Haemophilus ducreyi (chancroid)*
- *Chlamydia spp.*

GI Pathogens
- *Campylobacter spp.*
- *Helicobacter pylori*
- *Salmonella typhi*
- *Shigella spp.*

Miscellaneous Bugs
- *Arcanobacter spp.*
- *Bartonella henselae* (cat-scratch)
- *Bordetella pertussis*
- *Atypical mycobacteria*
- *Borrelia burgdorferi*
- *Babesia microti*

Macrolide Adverse Drug Reactions

- QTc Prolongation
  - Ery ≥ clarith > azith
- GI intolerance: nausea, bloating, diarrhea
  - Ery >> clarith >> azith
  - Dose related
  - Activity at motilin (peristalsis) receptors
  - Rare cholestatic hepatitis
- Pregnancy risk

Clindamycin Adverse Events

- Allergic reactions:
  - Rash, fever, erythema multiforme, anaphylaxis
- Elevated AST/ALT
  - Rare progression to severe liver injury
- Diarrhea
  - Can cause severe *C. difficile* toxin-mediated colitis
- Reversible neutropenia, thrombocytopenia, and eosinophilia
- Taste disturbance

Sanford Guide, Brit J Clin Pharmacol 64:542, 2007; Clin Med Insights Case Rep 2019 Dec 25;12:1-4

Thank You!

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- Kenneth Lawrence
- Evan Loh
- Paul McGovern
- Federico Perez
- Debra Poutsiaka
- George H. Talbot

Our patients and their families

Questions, Comments?

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