14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Helen W. Boucher, MD
Dean and Professor of Medicine
Tufts University School of Medicine
Chief Academic Officer, Tufts Medicine

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor: ID Clinics of North America, Antimicrobial Agents and Chemotherapy, Sanford Guide

Overview of Antibacterial Mechanisms

To Orient You: Little is Testable

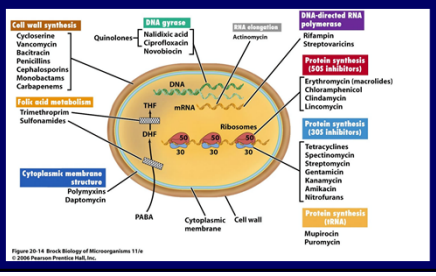


Figure 20-14 Brock Biology of Microorganisms 11/e
© 2006 Pearson Prentice Hall, Inc.

3

Cell Wall Active Agents

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

4

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

5

β-lactam Antibiotics Share Mechanism of Action

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

6

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

β-lactam Adverse Effects

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

7

Question

- What is the only cephalosporin active against MRSA

- A) Cefpodoxime
- B) Cefapime
- C) Ceftaroline
- D) Cefixime
- E) Cefoxitin

8

Question

- What is the only cephalosporin active against MRSA

- A) Cefpodoxime
- B) Cefapime
- C) Ceftaroline *
- D) Cefixime
- E) Cefoxitin

9

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**

10

Key Points About Cephalosporin Activity

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

11

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

12

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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

- 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

13

Vancomycin

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

14

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

15

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

Vancomycin for MRSA Bloodstream Infection

- Controversy re: optimal therapy – see Dr. Chambers lecture
- Vancomycin trough only monitoring no longer recommended
  - Target AUC/MIC_{BMD} 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

Drug Interactions

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

18

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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

19

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

20

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

21

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

22

Lipo/glycopeptide Testable Toxicities

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

23

Question

- Which quinolone has activity against MRSA

- A) Ciprofloxacin
- B) Moxifloxacin
- C) Trovafloxacin
- D) Delafloxacin
- E) Levofloxacin

24

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Question

- Which quinolone has activity against MRSA

- A) Ciprofloxacin
- B) Moxifloxacin
- C) Trovafloxacin
- D) Delafloxacin *
- E) Levofloxacin

25

Antibiotics Active Intracellularly

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

26

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**

27

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

28

Fluoroquinolone Pharmacokinetics

- **High oral bioavailability**
  - **>95% for moxi / levo, 70-80% for cipro**
- **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**

29

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++**

30

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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

31

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

32

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

33

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

34

Question

- 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

35

Question

- 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

36

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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

37

Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and 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

38

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

39

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*

40

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

41

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%

42

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

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*

43

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

44

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

45

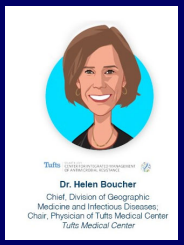
Thank You!

- Henry Masur
- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dudley
- Mike Dunne
- David Gilbert
- Susan Hadley
- Teena Kohli
- Kenneth Lawrence
- Evan Loh
- Paul McGovern
- Federico Perez
- Debra Poutsiaka
- George H. Talbot
- Our patients and their families

46

Questions, Comments?

- @hboucher3
- Helen.boucher@tufts.edu
- Helen.boucher@tuftsmedicine.org



47

Appendix

48

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Penicillins

Rx	Spectrum	Additional Adverse Events
Penicillin (oral/IV)	Group A strep; Syphilis	
Oxacillin/nafcillin (IV)	MSSA	AIN
Amoxicillin (oral) **Ampicillin** (IV)	Amox and amp have similar spectrum and are both broader than penicillin More active against H. flu, E. coli, Enterococcus, Listeria	
Amoxicillin clavulanate (oral) **Ampicillin sulbactam** (IV)	Broader spectrum than amox/amp due to addn of a beta-lactamase inhibitor; improved bioavilability (BID) Some activity against S. aureus; more active against H. flu and other gram negatives due to stability to some beta-lactamases NOT active against Pseudomonas Active against oral and gut anaerobes	Delayed hepatotoxicity (amox/clav)
Piperacillin tazobactam (IV)	Broader than amp/sulbactam Active against gram positive organisms including streptococci Broad activity against gram negatives incl Pseudomonas	

49

Cephalosporins

Rx	Spectrum	Additional Adverse Events
1st Gen Ceph •**Cefazolin** •**Cephalexin**	Staph and strep MSSA Some gram negatives including E. coli, Klebsiella, Proteus although 1st generation cephalosporins are very susceptible to beta-lactamases	
2nd Gen Ceph •**Cephamycin** •**Cefuroxime**	Gram positive cocci H. flu, E. coli, Klebsiella Cephamycin – active vs anaerobes, in vitro vs ESBLs (no clinical data)	
3rd Gen Ceph •**Ceftriaxone**	Streptococci pneumoniae (excellent) Gram negative rods but NOT Pseudomonas Excellent CSF penetration Drug of choice for bacterial meningitis	Biliary sludge
4th Gen Ceph •**Cefepime**	Broad gram positive and broad gram negative activity, including Pseudomonas Often used as empiric therapy in hospitalized patients (however may need to add vancomycin to treat MRSA)	Potential neurotoxicity, especially in patients with renal failure
5th Gen Ceph •**Ceftaroline**	Broader than amp/sulbactam; ceftriaxone-like Prodrug Active against gram positive organisms including streptococci and broad activity against gram negatives not incl Pseudomonas	

50

Ceftaroline Clinical Use

- **Acute bacterial skin and soft tissue infections**
- **Community Acquired Pneumonia**
- ***S. aureus* bloodstream infection**
  - **Controversial-see Chambers Lecture**
- **Controversy over dosing regimen**
  - **600mg twice daily – FDA-approved regimen**

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156; File et al. CID 2010; 51: 1395; Zasowski et al, AAC 2017;61(2),e02015-16; Gerlak et al. AAC 2019; 63(5); Kalil et al. AAC 2019; 63(11)

51

Ceftaroline Safety and Monitoring

- **Hypersensitivity 1-3%, rash 3%**
- **GI - nausea, vomiting, diarrhea 5%**
- **Hematologic toxicity (class effect)**
  - **Eosinophilia**
  - **Positive Coomb's test, rarely clinically significant**
- **Hepatotoxicity – LFT abn 1-7%**
- **Nephrotoxicity rare**
- **Neurotoxicity – tremor, confusion, seizure, encephalopathy**
  - **Worse with renal failure**

52

Oritavancin - Lipoglycopeptide With Long Half-life

- **Mechanism of action**
  - **inhibition of cell wall synthesis and disrupts bacterial membrane**
  - **Gram-positive spectrum**
    - ***S. aureus*, MRSA, VISA, VRSA, GAS, *S. anginosus* group**
    - ***E. faecalis* , *E. faecium*/VRE (active vs VanA, VanB, Van C, Van D)**
- **Bactericidal**
- **IV only, 1 dose**
  - **1200 mg over 3 hours**
- **Cytochrome P450 enzyme – warfarin interaction**
- **FDA approved**
  - **ABSSSI**

HF Chambers NEJM 2014; 370(23): 2238. WWW.FDA.GOV, Arias et al CID 2012: 54 (Suppl 3): S233; GR Corey et al. NEJM 2014; 370(23): 2180-2190

53

Dalbavancin - Lipoglycopeptide With Long Half-life

- **Gram-positive spectrum**
  - ***S. aureus*, MRSA, VISA, GAS**
  - **Low MRSA MICs**
  - **Enterococci – inactive vs VanA**
- **Mechanism of action – cell wall synthesis inhibit**
- **Bactericidal**
- **IV only (dose over 30 min), long half-life (app 8.5 days)**
- **Dosing**
  - **1000mg, then 500mg every 7 days OR 1500mg x 1**
  - **Decrease dose by 25% for CrCl <30ml/min, not dialysis**
- **FDA approved ABSSSI**

Dowell et al. *Critical Care* 2008, 12(Suppl 2):P26. www.fda.gov
Nailor and Sobel. Infect Dis Clin N Am 23(2009); 965. Jauregui et al. CID 2005; 41: 1407; Dunne et al CID 2016
HW Boucher, M Wilcox, GH Talbot, S Puttagunta, AF Das, MW Dunne. NEJM 2014; 370(23): 2169

54

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD

Dalbavancin

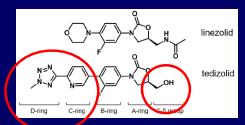
- Other uses
  - Limited data, varying dosing regimens
    - Endocarditis and osteomyelitis
    - Persons who inject drugs
- Case reports of failure with emergence of VISA, presumably associated with low-level drug exposure
  - One patient had VISA detected in urine while on dalbavancin for CLASBI
  - One patient was pregnant and had failure of therapy for IE

• Steele JM et al. J Clin Pharm Ther. 2018;43:101-103.
• Werth BJ et al. Clin Microbiol Infect. 2018;24:429.e1-429.e5.

55

Tedizolid - Oxazolidinone Drug Class Once Daily Dosing, Lower Dose

- Non-antibiotic antibacterial; a MAO inhibitor
  - Inhibits protein synthesis, bactreiostatic
    - Binds peptidyl transferase region of bacterial ribosome prevents binding of amino acyl tRNA
- Gram-positive spectrum
  - *S. aureus*, MRSA, VISA, GAS, *S. agalactiae*, *S anginosus* group, *E. faecalis* (vanco-susceptible only)
- IV and oral
- Half-life 12 hours, once daily dosing
- 200 mg daily x 6 days
  - No dose adjustment for age, renal/hepatic impairment
- FDA approved ABSSSI
- HABP/VABP Study Failed



Moellering CID January 2014; Wunderink; Prokocimer et al. JAMA 2013; Moran GJ, et al. *Lancet Infect Dis.* 2014;14:696-705; CID 2021

56

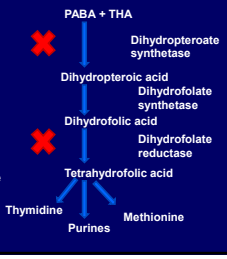
Sulfonamides & TMP/SMX

- 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

57

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



58

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

59

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

60

14 – Core Concepts: Antibacterial Drugs II Gram Positive Organisms

Speaker: Helen Boucher, MD