Antibiotic Update

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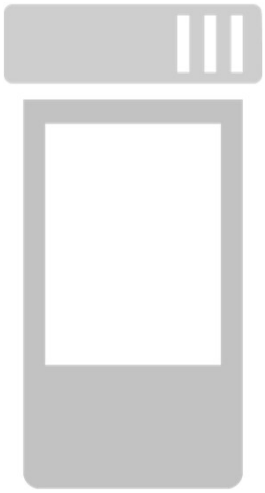
Objectives

- Updated understanding of antimicrobial recommendations and available treatment options in 2026
- Provide a clinical scenario followed by an update on antibiotics pertinent to the following topics
    - UTI
    - Pneumonia
    - C diff
    - SSTI
- QR codes on slides link to relevant articles for further reading

Antimicrobial Stewardship



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Educated decision

Correct Patient

Correct Indication

Correct Drug

Correct Dose

Correct Duration

Antimicrobial Stewardship

Antimicrobial Trends

- Overall, antimicrobial duration recommendations have been steadily decreasing

Antimicrobial Trends

Diagnosis	2026	Prior
CAP	3 - 5 d	5 - 14 d
VAP	5 - 8 d	10 - 15 d
Pyelonephritis	5 - 7 d	10 - 14 d
Gram negative bacteremia	7 d	14 d
Cellulitis	5 - 7 d	10 d
Osteomyelitis	42 d	84 d
Intra-abdominal infections	4 d	8 - 10 d

Antimicrobial Trends

- Overall, antimicrobial duration recommendations have been steadily decreasing
- Some instances, antibiotics deferred for first line treatments with supportive care prioritized
  - Diverticulitis, Acute otitis media

47 y/o presents with 2 days of dysuria, increased urinary frequency, and urgency. Appropriately started on cephalexin but symptoms fail to resolve 4 days later. The urine culture is growing ESBL E coli. Which is the best plan?

A. Oral nitrofurantoin
B. Oral amoxicillin-clavulanate
C. Oral sulopenem etzadroxil-probenecid
D. Send to the hospital for IV ertapenem
E. Send to ER for single dose of IV aminoglycoside

UTI w/ ESBL producing Bacteria

- Fosfomycin
- Amoxicillin-clavulanate
- Nitrofurantoin
- Ciprofloxacin
- Trimethoprim – Sulfamethoxazole
- Newer options

Nitrofurantoin

- Pharmacology
  - Well absorbed
  - Appreciable concentrations in **urine** ONLY
- **Cystitis**!!!! [NOT pyelonephritis]
  - ONLY if CrCl >50
- Duration for uncomplicated cystitis = 5 days
- Risk of pulmonary fibrosis / ILD in prolonged use

Fosfomycin

- Pharmacology
  - Renal elimination, no systemic use outside of urinary tract
- UTIs with specific organisms
  - VRE, ESBL-producing organism and KPC-producing organism
- 3 gm oral dose **x 1**
- Challenging to find at pharmacy & can be expensive. Difficult to get MIC

Trimethoprim-sulfamethoxazole

- High concentration in the urinary tract
- UTIs duration is only 3 days

Amoxicillin-clavulanate

- In some cases, this is an effective oral antibiotic even if the pathogen is an ESBL-positive organism as the clavulanic acid inhibits some beta lactamases.
  - Patients with very high MIC may fail
  - Potentially avoids hospitalization if clinical response can be monitored closely
  - Would reserve for non-febrile patients
- Adverse effects = diarrhea, abdominal cramping

NEW UTI Antimicrobials

- sulopenem + probencid (Orlynvah™)
  - FDA approved Fall 2024
- gepotidacin (Blujepa™)
  - FDA approved March 2025

Sulopenem etzadroxil-probenecid

- A penem antibacterial that works by inhibiting bacterial cell wall synthesis through binding to penicillin-binding proteins (PBPs).
- Combined with probenecid, a renal tubular inhibitor blocks OAT3-mediated renal clearance, leading to increased plasma concentrations of the active drug.
- FDA approved indication for **uncomplicated UTI**

Sulopenem etzadroxil-probenecid

- **REASSURE trial**
  - "Sulopenem versus Amoxicillin/Clavulanate for the Treatment of Uncomplicated Urinary Tract Infection"
  - randomized, double-blind, non-inferiority trial
  - Enrolled over 2000 woman

Sulopenem etzadroxil-probenecid

- **REASSURE trial**

Primary Endpoint	Sulopenem-pro	Amox-clav
Micro-MITT population	318/522 (60.9%)	260/468 (55.6%)
	Treatment difference +5.4% Met criteria for non-inferiority	
Micro-MITT-R (resistant)	22/42 (52.4%)	17/25 (68%)
	Treatment difference -15.6% Lower success rate for resistant infection, though wide confidence interval and small sample size	

Sulopenem etzadroxil-probenecid

- **REASSURE trial**
  - Adverse events occurred more frequently in sulopenem group compared to amox-clav
    - Mild-moderate, no serious adverse events
    - Most common: **diarrhea**, nausea, headache

Sulopenem etzadroxil-probenecid

- **SURE-1 trial**
  - Uncomplicated UTI in1660 woman compared to oral ciprofloxacin
  - Results:
    - **Non-inferior compared to ciprofloxacin**
    - Superior to cipro in patients with cipro resistance
    - Not non-inferior in cipro-susceptible pathogens

Sulopenem etzadroxil-probenecid

- **SURE-2 trial**
  - Hospitalized patients complicated UTI, randomized
    - 5 days of IV sulopenem followed by oral sulopenem

      OR
    - 5 days of IV ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate

Sulopenem etzadroxil-probenecid

- **SURE-2 trial**
  - Primary endpoint: Overall test of cure composite
    - Clinical outcome: baseline signs/symptom resolved
    - Micro outcome: negative blood culture & urine pathogen culture $10^5 \rightarrow 10^3$

Results	**Sulopenem** (n = 444)	**Ertapenem** (n= 440)
Primary Endpoint	67.8%	73.9%
	Treatment difference -6.1%	
Secondary endpoint - Clinical response	89%	88%

Sulopenem etzadroxil-probenecid

- **SURE-2 trial**
  - Sulopenem NOT non-inferior to ertapenem
  - Caveats:
    - 5 days of IV sulopenem aka didn't avoid hospital
    - Not meeting criteria partially is based on asymptomatic bacteriuria

Sulopenem etzadroxil-probenecid

- Take aways:
  - More GI side effects compared to amox-clav
  - Rather concerned about increased rate of CRE
  - Drug interactions due to probenecid
  - Very expensive
    - ~$300 per pill x 5 days q12 = $3,000 per course
  - Not yet convinced of clinical benefit

Gepotidacin

- Novel triazaacenaphthylene antibacterial, which inhibits type II topoisomerases, including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, resulting in inhibition of DNA replication
- FDA approved for uncomplicated UTI

Gepotidacin

EAGLE-2 & EAGLE-3

- Oral gepotidacin vs nitrofurantoin with uncomplicated UTI.
- 2 randomized, controlled, double blind, double dummy non-inferiority trial. Woman only

Primary Endpoint: Therapeutic success	**gepotidacin**	**nitrofurantoin**
EAGLE-2	162/320 (50.6%)	135/287 (47%)
EAGLE-3	162/277 (58.5%)	115/264 (43.6%)

Gepotidacin

EAGLE-2 & EAGLE-3

- Oral gepotidacin non inferior to nitrofurantoin with uncomplicated UTI.
- Adverse drug reactions: Diarrhea, nausea
- CYP3A4 drug interactions
- Interaction with cholinergic/anticholinergic drugs
    - ***oxybutynin***

Gepotidacin

EAGLE-1 Trial

- Oral gepotidacin vs IV ceftriaxone for gonorrhea
  - Demonstrated non-inferiority

Gepotidacin

- Take aways
  - Only for uncomplicated UTI
  - May be alternative if resistance patterns or adverse event / drug allergy prevents use of other drugs
    - No MIC data available currently
  - Very expensive
    - $87 per tablet, 2 tabs q12 x 5 days = $1750
  - Might end up more useful for gonorrhea

IV aminoglycoside single dose

- Old drug with NEW tricks!
- Single dose for treatment of UTI
  - Eliminates need for patient adherence
  - Averts need for inpatient admission due to lack of susceptible oral antibiotic
- Peak urine concentrations HIGH, present for 72+ hours
- Tailor drug selection based on MIC
  - Amikacin, gentamicin, tobramycin

IV aminoglycoside single dose

- Old drug with NEW tricks!
- Not to be utilized for bacteremia, aminoglycoside resistant pathogens, or pyelonephritis
- Challenges
  - May still need to direct patient to ED or infusion center to receive a dose
  - More variability in dosing as weight based – protocols help

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35 y/o presents with 4 days of productive cough and 24 hours of fevers. Chest X-ray notes RML consolidation. Influenza and COVID tests are negative. Rapid Strep +. Which antimicrobial regimen is best option?

A. Amoxicillin for 3 days
B. Amoxicillin for 14 days
C. Levofloxacin for 5 days
D. Amoxicillin-clavulanate + doxycycline for 5 days
E. Admit for IV antibiotics

Pneumonia duration

- 2016 JAMA - Duration of Abx in CAP
  - 5 days Abx for CAP

- 2021 Lancet – double blind, randomized, placebo
  - 3 days Abx for CAP

- Multitudes of other similar studies

Evidence indicates **3-5 days** of antimicrobials is sufficient for pneumonia

NEW-er Pneumonia Antimicrobials

- Lefamulin (Xenleta™)
  - FDA approved 2019
- Omadacycline (Nuzyra™)
  - FDA approved in 2018

Lefamulin

- Spectrum of activity: MSSA, Strep pneumoniae, H. influenza, Legionella, Mycoplasma pneumoniae & Chlamydophila pneumoniae
  - But much broader coverage in reality: E faecium (including VRE), MRSA/VRSA, MDR S. pneumonia, fastidious gram negatives, oral anaerobes & atypical coverage
- Unclear if/how this drug will be utilized.
- Pricing not listed on GoodRx

Omadacycline

- IV & oral options
- Like minocycline but enhanced potency against gram positive and atypicals
- Approved for SSTI & CAP
- May be difficult to obtain
  - •Unclear advantages at this time & expensive
  - •Potential alternative to FQ for CAP in the future
- Pricing not listed on GoodRx

	Doxycycline	Minocycline	Tigecycline	Omadacycline	Eravacycline
MS/RSA	++	++	+++	+++	+++
S. pneumoniae	+/-	+/-	+++	+++	+++
E. faecalis	+/-	+/-	+++	+++	+++
E. faecium, including VRE	+/-	+/-	+++	+++	+++
H. influenzae, M. catarrhalis	++	++	+++	+++	+++
K. pneumoniae and E. coli, including CRE and ESBL *bla*	+/-	+/-	++	+	+++
Enterobacter cloacae	+/-	+/-	++	+	+++
Proteus spp	0	0	0	0	+/-
Pseudomonas aeruginosa	0	0	0	0	0
Acinetobacter spp	0	++	++	++	+++
Stenotrophomonas malt.	0	++	+	+	++
Atypicals	++	++	++	+++	+++
Anaerobes	0	0	++	++	++

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D. Amoxicillin-clavulanate + doxycycline for 5 days
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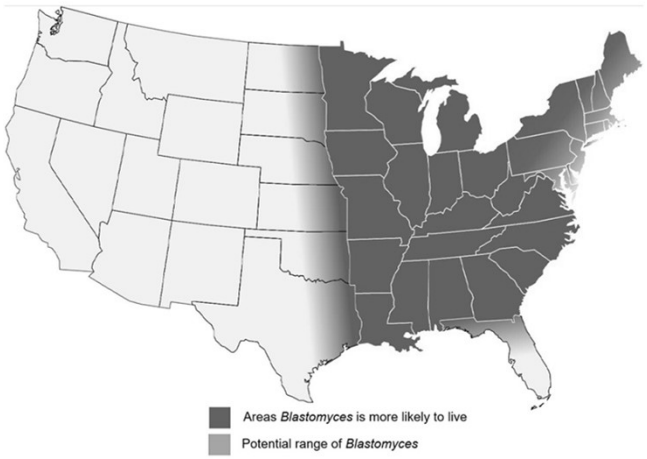
35 y/o initially presented with 4 days of cough and fevers. Chest X-ray notes multifocal pneumonia. Flu and COVID negative.

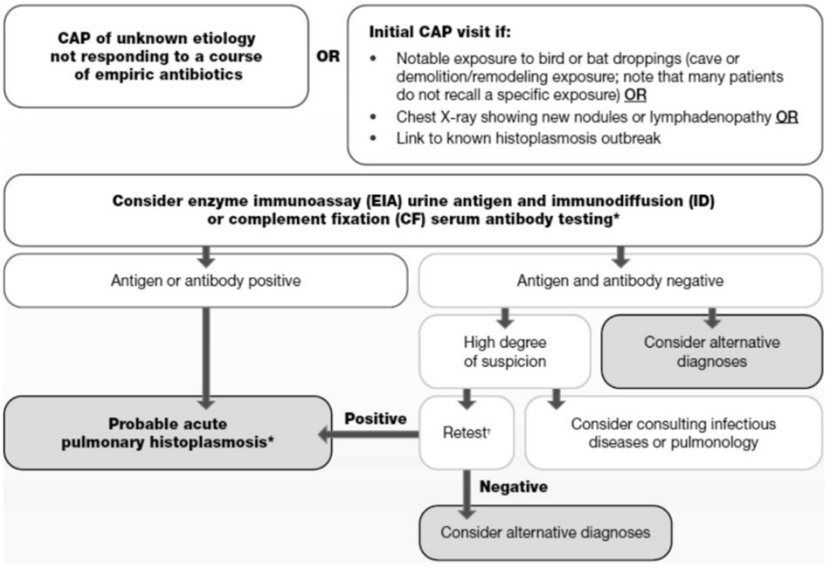
Given a course of doxycycline but now 12 days later continues to have intermittent fevers, night sweats and cough.

What are the next best steps?

Endemic fungal pneumonia



CDC - Histoplasmosis algorithm



Histoplasmosis

- Differential in patients with high fevers, respiratory symptoms and minimal response to antibiotics
- Immunocompromised patients, especially on newer biologics & TNF inhibitors may become very ill
- Most immunocompetent patients recover without needing any antifungal treatment

35 y/o initially presented with 4 days of cough and fevers. Chest X-ray notes multifocal pneumonia. Given a course of doxycycline but now 12 days later continues to have intermittent fevers, night sweats and cough. What are the next best steps?

A. Start on levofloxacin
B. Start on itraconazole
C. **Order histo antigen of urine & serum**
D. Order histo comp-fixation antibody

63 y/o presents with 10-12 liquid diarrhea, abdominal pain and fever. Patient recently prescribed clindamycin for bilateral LE cellulitis. Episode of C diff treated 6 months ago. Testing including C diff PCR and toxin return positive. What treatment should be initiated?

A) Oral vancomycin

B) IV vancomycin

C) Oral fidaxomicin

D) IV metronidazole

E) Oral vancomycin + emergent FMT

C diff colitis antibiotics

Oral vancomycin

OR

Oral fidaxomicin

C diff colitis – Oral vancomycin

- When administered orally, bioavailability is extremely poor, essentially not systemically absorbed allowing for high concentration in colon
- **Dosing: 125 mg every 6 hours for 10 days**

- Higher doses have been linked to risk of candidemia and bacteremia due gut translocation related to drug-induced tissue damage.
- Vanco taper may be utilized as well

C diff colitis – Oral fidaxomicin

- Oral macrolide with minimal GI absorption
  - Bactericidal activity against C diff, Staph, Enterococci, minimal activity against gram negative & fungi
  - Cannot be used for systemic infections
- Dosing: 200 mg every 12 hours for 10 days
- Some studies suggest for recurrent C diff, may utilized fidaxomicin pulse
  - 200 mg every 12 hours x 5 days,
  - then 200 mg every other day x 20 days

Vancomycin versus fidaxomicin

Study in NEJM in 2011 phase 3 trial

	Fidaxomicin	Vancomycin	P value
Clinical cure			
mITT	88.2	85.8	
PP	92.1	89.8	
Recurrence			
mITT	15.4	25.3	0.005
PP	13.3	24	0.004
Global Cure			
mITT	74.6	64.1	0.006
PP	77.7	67.1	0.006

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Global Cure			
mITT	74.6	64.1	0.006
PP	77.7	67.1	0.006

Vancomycin versus fidaxomicin

Study in CID in 2011 compared

No CA*	Fidaxomicin	Vancomycin	P value
Clinical cure			
Treatment	92.3% (361/391)	92.79 (386/416)	.8
Recurrence			
Treatment	12.23 (40/327)	23.42 (78/333)	<.001
Follow-up	11.52 (38/330)	23.88 (80/335)	<.001
anytime	11.92 (36/302)	23.12 (71/307)	<.001
Global Cure			
At anytime	80.8 (282/349)	69.07 (259/375)	<.001

*CA = concomitant Antibiotics. Similar comparison with CA was not statically significant

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Vancomycin versus fidaxomicin

- Meta-analysis in 2022 by Tashiro et al
  - Six randomized controlled trials included
  - There was no significant difference observed for clinical cure rates of initial infection (p = 0.31)
- Meta-analysis in 2024 by Zhao et al
  - No significant difference between vancomycin & fidaxomicin in treatment for effectiveness and adverse reactions
  - Fidaxomicin superior to vancomycin in recurrence rate and long term mortality
  - Vancomycin more effective for severe CDI

Vancomycin versus fidaxomicin

- Fidaxomicin has been very expensive in the past. Though pricing slowly improving
- A10 day course on 3/1/2026 per GoodRx

Vancomycin	Fidaxomicin
$73.32	$2,465

C diff colitis antibiotics

Metronidazole

Previously a drug option, studies and clinical experience have shown decreased efficacy for clinical cure and resolution of diarrhea (P=0.02)

2018 IDSA/SHEA guidelines removed metronidazole as treatment for CDI

IV Metronidazole now used in combination with oral vancomycin for fulminant C diff OR in setting of ileus

No longer available "Antimicrobials"

- **Bezlotoxumab**
  - monoclonal antibody against C diff toxin B to prevent recurrence in high risk patients.
  - No longer available
- **Fecal Microbiota Transplant with Open Biome**
  - Instilled via colonoscopy or NG tube
  - no longer available

NEW-er C diff "Antimicrobials"

Fecal Microbiota Therapies – donor derived

Considered AFTER successful treatment of recurrent CDI to prevent further recurrence (restorative)

- **Vowst™** (fecal microbiota spores, live-brpk) capsule
- **Rebyota™** (fecal microbiota, live-islm) suspension for rectal use

NEW-er C diff "FMT"

Vowst™	Rebyota™
Oral capsules	Enema
48 to 96 hours after completing CDI treatment	24 to 72 hours after completing CDI treatment
Must drink 10 oz magnesium citrate the day before Dose is 4 capsule daily x 3 days Must be taken on empty stomach prior to first meal of the day	150 mL enema, rectal administration ONLY.
Self administered	Generally administered in clinic

Treatment Strategy stratifying

Risk factor for recurrence

- Age > 65 years
- Broad spectrum antibiotic during or within 1 month after C diff treatment
- Immunocompromised
- PPI use
- Severe CDI with CDI score >3

Severity of illness Score for CDI (>3 points = severe)

- Fever
- Ileus
- Systolic BP <100
- WBC > 15K; additional point if WBC >30
- CT findings of thickened colonic wall, colon dilation, ascites; additional point if 2 findings

C diff treatment strategy

Diagnosis	<2 risk factors	>3 risk factors
Initial Episode of CDI	Oral vancomycin	Fidaxomicin
First Recurrence of CDI	Vancomycin taper OR Fidaxomicin	Vancomycin taper OR fidaxomicin pulse
Second Recurrence of CDI	Vancomycin taper OR fidaxomicin pulse based on previous treatment history Restorative FMT could be considered	
Fulminant Colitis	Add IV metronidazole AND rectal vancomycin	

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If another recurrence would consider FMT products after treatment

53 y/o presents with left lower extremity erythema and pain. Noted to have induration and edema on exam. Started on trim-sulfa but after 5 days has progression of symptoms. What are the best next steps?

A) Start oral cephalexin + doxycycline

B) Start oral linezolid

C) Admit to the hospital for IV vancomycin

D) Admit to the hospital for IV daptomycin

E) Give a single dose of IV dalbavancin

MRSA SSTI Antimicrobials

- Trimethoprim/Sulfamethoxazole (TMP/SMX)
- Doxycycline
- Clindamycin
- Linezolid
- Delafloxacin

+/- Addition of Strep coverage

Trim-sulfa

- SSTI ⇒ Normal CrCl Dosing: 1 DS BID if <80 kg and 2 DS BID if >80 kg
  - •Purulent alone
  - •Non-purulent combine
- UTI

Trim-sulfa --- Adverse Effects

Hypersensitivity

Nephrotoxicity

- Asymptomatic increase in serum creatine (inhibition of renal tubular secretion)
- Hyperkalemia (increased risk with ACEi/ARB use)
- Interstitial nephritis, crystalluria

Bone marrow suppression / Neutropenia

Aseptic meningitis

SJS/ TEN

Drug interactions → warfarin, phenytoin

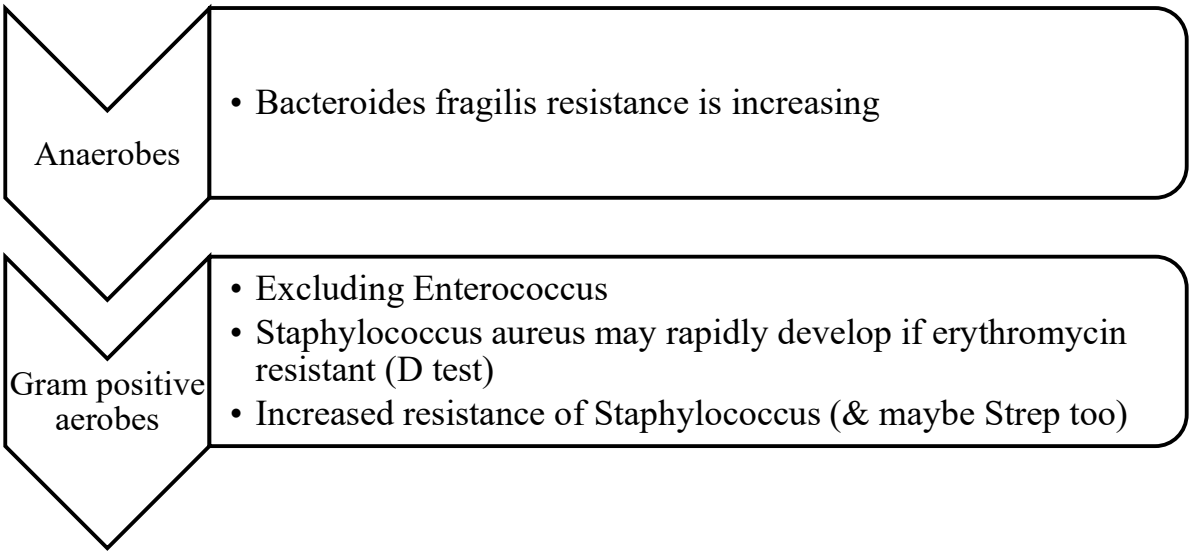
Doxycycline

- SSTI
  - Purulent alone
  - Non-purulent combine with better Strep drug
- Pharmacokinetics
  - High oral bioavailability (90%)
  - Binds to divalent & trivalent cations
  - Caution with co-administration of meds & supplements
  - Widely distributed

Doxycycline

- Photosensitivity
- Pill esophagitis
  - avoid lying down for 30 minutes after dose
- Nausea/ vomiting
  - improved by taking w/ food
- Discoloration of teeth
  - Contraindicated in pregnancy & age < 8 years
- Nephrogenic diabetes inspipidus
  - Demeclocyline (used for SIADH)

Clindamycin



Clindamycin – Adverse Effects

C difficile colitis

***GI intolerance ***

- Nausea, vomiting, bitter taste

Hypersensitivity

- Rash, drug fever, eosinophilia, anaphylaxis

Linezolid

- SSTI
- Pharmacology
  - Great absorption, ~100% bioavailable
  - Great tissue penetration
- Also has **anti-toxin** activity if unable to use clindamycin for necrotizing fasciitis
- Becoming more affordable. GoodRx $33 for 7 days

Linezolid – Adverse Effects

Bone marrow suppression (reversible)

- Thrombocytopenia & leukopenia
- Usually when used for >2 weeks

Neuropathy if given for long periods (>6-12 weeks)

- Optic - usually reversible
- Peripheral – painful sensory, may persist

CNS

- headache, insomnia

Increased risk for Serotonin syndrome

- When used with other agents: SSRI, TCA, etc.
- Increased risk with high doses, increased # of drugs & older age of drug

Dalbavancin

- FDA approved in 2014 for complicated SSTI
- Dosing- one time infusion for SSTI
- Option for failed oral treatment for SSTI
  - Covers MRSA & VRE (+/- VanB)
- Expensive, but access improving especially in ED if avoids hospitalization

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