Antibiotics Update

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Goals

- Briefly discuss antibiotic overuse
- Provide a clinical scenario followed by a update on antibiotics pertinent to the topic
- In order to complete this is time, will not covering the following:
  - Drug dosing (except rare instances), mechanism of action, in-depth pharmacokinetics
  - Certain classes of antibiotics:
    - Vancomycin
    - Oral cephalosporins gen 2 & 3
    - IV cephalosporins gen 1-4
    - IV Penicillins
    - Aminoglycoside
    - Polymyxins

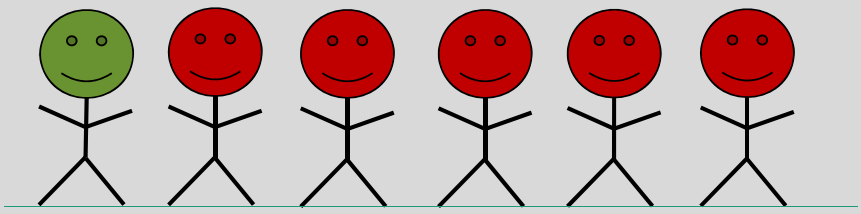
Ambulatory Antimicrobial Stewardship

A collaborative response to combating antibiotic resistance & improve patient safety

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

In 2014, **266.1 million courses** of antibiotics dispensed to outpatients in U.S. community pharmacies.

This equates to more than 5 prescriptions written each year for every 6 people in the United States.

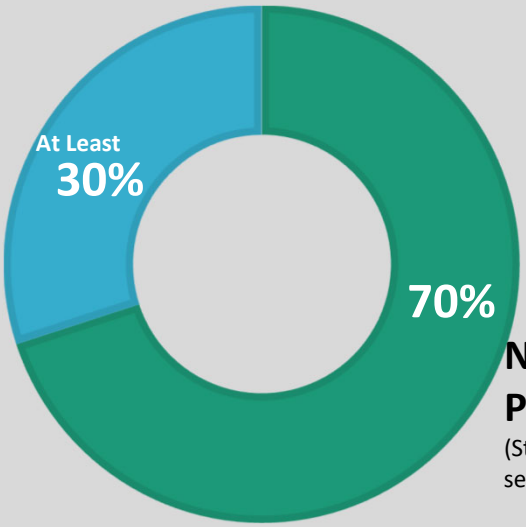


Centers for Disease Control and Prevention. Outpatient antibiotic prescriptions — United States, 2014

In U.S. Doctor's Offices & Emergency Departments

ANTIBIOTIC USE

Unnecessary Prescriptions



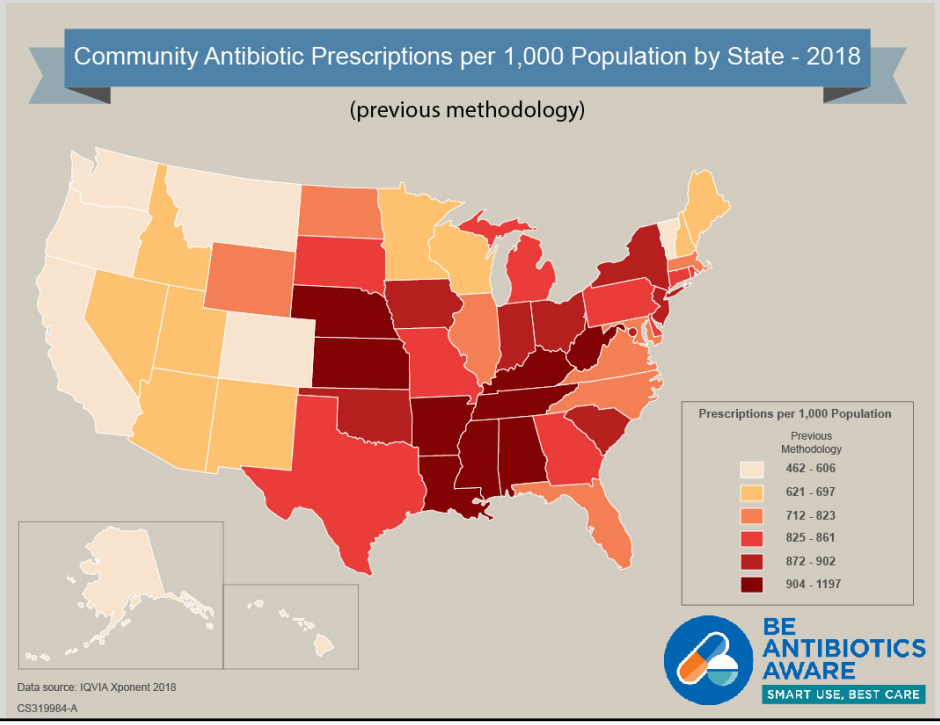
Necessary Prescriptions
(Still need improvement on drug selection, dose & duration)

Fleming-Dutra et al. JAMA 2016;315(17):1864-1873.

Total inappropriate antibiotic use

50%

- **Unnecessary use**
- **Inappropriate antibiotic selection**
- **Inappropriate antibiotic dosing**
- **Inappropriate antibiotic duration**



Now… the Antibiotics!

A 40 y/o man is admitted to the hospital for left toe osteomyelitis. His bone culture grows a pan-susceptible strain of E coli.

Which of the following is NOT a contraindication to use of an oral fluoroquinolone for treatment?

A. History of QTc >500
B. History of Aortic Aneurysm
C. History of Diabetes Mellitus
D. History of Myasthenia Gravis
E. History of Achilles tendon injury

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Fluoroquinolones

Ciprofloxacin, Levofloxacin, Moxifloxacin, Delafloxacin

Fluoroquinolones (FQ)

The Good

+ Broad spectrum of activity
+ Large volume of distribution
+ High oral bioavailability

- Increasing resistance
- Serious Adverse events, including C diff
- 2016 FDA Safety Warning

The BAD

→**Conclusion**

→**AVOID for uncomplicated infections**

→**Severe infections - Risk versus Benefit**

FQ Pharmacology

- Excellent oral bioavailability (59-95%)
- Good tissue, bone, lung and CNS penetration
- Chelation by **divalent cations** decreases bioavailability
  - **Avoid dosing with Calcium, Iron, Zinc, Magnesium, Aluminum**
  - → **Including nutrient supplements, like Ensure**
  - Administer FQ 2 hours before or 4 hours after if needed
- Highly renally eliminated (except moxifloxacin)

FQ - Spectrum of Activity

Bacteria	Ciprofloxacin	Levofloxacin	Moxifloxacin	Delafloxacin
Enterobacterale	++++	+++	+++	+++
Ps. aeruginosa	++++	++	-	++
Strep pneumoniae	+	++++	++++	++++
MRSA	-	-	-	++++ (20% "R")
Anaerobes	-	-	++++	++
Mycobacteria	-	++++	++++	-
Anthrax	++++	++++	++++	++++

FQ – Clinical uses

Common Uses	Ciprofloxacin	Levofloxacin	Moxifloxacin	Delafloxacin
Pneumonia		★	★	?
Intra-abdominal infection	★ w/ metronidazole	★ w/ metronidazole	★	
UTI / pyelo	★	★		
Prostatitis	★	★		
Complicated SSTI	★	★	★	★
Osteomyelitis	★	★	★	?

FQ – Clinical pearls

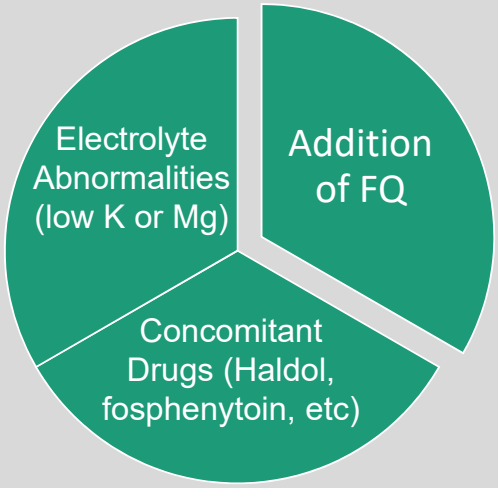
Pearl	Ciprofloxacin	Levofloxacin	Moxifloxacin	Delafloxacin
One-word	Pseudomonas	Respiratory	Anaerobes	MRSA
Pseudomonas	Preferred FQ (when susceptible)	Less potent P. aeruginosa activity	No coverage	Yes
Respiratory	No	Great respiratory FQ	Great respiratory FQ	?
UTI	Second line	Second line	**NO**!	?
Gram negative Bacteremia	Step down	Step down		
Oral Dosing	Twice daily	Once daily	Once daily	Twice daily

FQ - Adverse Effects

GI	• N/V • Abdominal discomfort • LFT abnormalities
CNS	• Headache • Dizziness • Insomnia • Delirium
CV	• QTc prolongation / Torsades • Aortic Aneurysm
MSK	• Arthropathy • Tendinitis / rupture
Derm	• Phototoxicity • Rash • Urticaria / Angioedema

FQ – QTc Prolongation

- None of the FQs are high risk alone
- If using for a long duration, would recommend obtaining EKG prior to treatment for baseline
- Lowest risk with Delafloxacin



FQ - FDA Warnings…

- **July 2008**: tendonitis / tendon rupture
- **February 2011**: myasthenia gravis exacerbation
- **August 2013**: irreversible peripheral neuropathy
- **May 2016**: Restrict use for certain uncomplicated infections
- **July 2016**: disabling side effects of tendon / nerve / muscle / joint & CNS with possibly permanent side effects
- **July 2018**: Mental health & hypoglycemia
- **December 2018**: increased risk for aortic aneurysm & dissections

A 25 y/o man presents to his PCP with a "boil" on his back for the past 5 days with surrounding erythema & a well demarcated border.

After I&D, which antibiotic listed below would you NOT prescribe for his purulent cellulitis?

A. Clindamycin
B. Doxycycline
C. Trimethoprim-Sulfamethoxazole
D. Cephalexin
E. Linezolid
F. Delafloxacin

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E. Linezolid
F. Delafloxacin

MRSA Antibiotics

Oral

- TMP/SMX
- Doxycycline
- Clindamycin
- Linezolid
- Delafloxacin
- Lefamulin

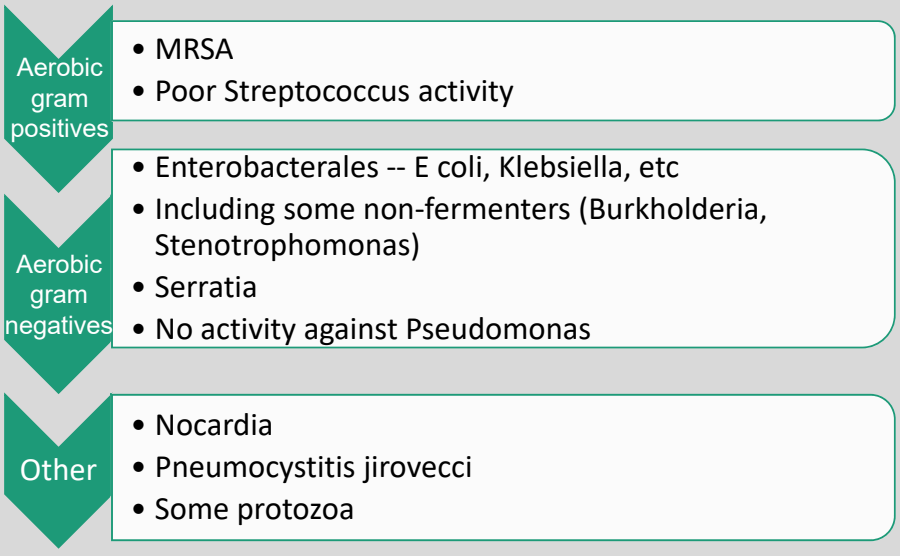
Parenteral

- Vancomycin
- Daptomycin
- Ceftaroline
- Telavancin / ortiavancin/ dalbavancin
- Tigecycline
- Quinupristin / dalfopristin

Trimethoprim/Sulfamethoxazole

TMP/SMX (Bactrim)

TMP/SMX - Spectrum of Activity



TMP/SMX - Pharmacology

- Great oral absorption (90-100%)
- Widely distributed including CNS, Bone & Prostate
- Bacteriostatic
- Several drug-drug interactions

TMP/SMX - Clinical use

- **SSTI**
  - **Purulent alone**
  - **Non-purulent combine**
- UTI
- PCP prophylaxis

Normal CrCl Dosing:
1 DS BID if <80 kg and
2 DS BID if >80 kg

- IV form occasionally in hospital
  - PCP treatment, Nocardia & Steno
  - Very large fluid load (0.5 to 1L per dose)

TMP/SMX – Adverse effects

- Hypersensitivity
- Nephrotoxicity
  - Asymptomatic increase in serum creatine (inhibition of renal tubular secretion)
  - Hyperkalemia (increased risk with ACEi/ARB use)
  - Interstitial nephritis, cystalluria
- Bone marrow suppression / Neutropenia
- Aseptic meningitis
- SJS/ TEN
- Drug interactions → warfarin, phenytoin

Tetracycline

(Part 1)
Tetracyline, doxycycline, minocycline

(Part 2)
tigecycline
eravacyline, omadacycline

Tetracycline - Pharmacology

- High oral bioavailability (90%)
- Binds to divalent & trivalent cations
  - Caution with co-administration of meds & supplements
- Widely distributed

Tetracycline – Spectrum of Activity

- Aerobic & facultative anaerobic bacteria
- Minocycline & doxycycline most active against Staphylococci, including MRSA
- Minimal activity against Strep
- Atypical coverage (Chlamydia & Mycoplasma)
- Rickettsiae
- Spirochetes
- Some Protozoa & Mycobacteria

Tetracycline – Clinical Use

Doxycycline	Minocycline	Tetracycline
SSTI (purulent alone)	MDR Acinetobacter baumannii	H. Pylori
Atypical coverage for pneumonia		
Arthropod borne infections*		
Latent Syphilis		

Tetracycline – Adverse Effects

- 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 - Pharmacology

- Absorption is rapid & complete
- Penetrates most tissues, except CSF

Clindamycin – Spectrum of Activity

Anaerobes

- Bacteroides fragilis resistance is increasing

Gram positive aerobes

- Excluding Enterococcus
- Staphylococcus aureus may rapidly develop if erythromycin resistant (D test)
- Increased resistance of Staphylococcus (& maybe Strep too)

Clindamycin – Clinical use

- SSTI
- Anaerobic pulmonary infection
- Hospital – inhibition of GAS toxin production in necrotizing fasciitis

Clindamycin – Adverse Effects

C difficile colitis

***GI intolerance ***

- Nausea, vomiting, bitter taste

Hypersensitivitiy

- Rash, drug fever, eosinophilia, anaphylaxis

Linezolid / Tedizolid

Linezolid– Pharmacology

- Great absorption, 100% bioavailable
- Great tissue penetration

Linezolid– Spectrum of Activity

Gram positive Aerobes

- Staphylococcus spp.
- Streptococcus spp.
- Enterococci (faecium & faecalis); including **VRE**

Misc

- Mycobacterium sp.
- Nocardia sp.

→ **Try to reserve for MDR Gram positive**

Linezolid– Clinical use

- Pneumonia – MRSA
- VRE infections
- Complicated skin infections
- Alternative for MRSA & VRE infections
- Also has **anti-toxin** activity if unable to use clindamycin for necrotizing fasciitis

<u>The downsides</u>

- Expensive $$$
- Try to AVOID in bacteremia, as inferior outcomes noted

Linezolid– Adverse Events122

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

Tedizolid

- Similar to linezolid
- Active against linezolid-resistant Staph aureus
- Maintains coverage against VRE
- Clinical use - SSTI

- Theoretically, less bone marrow toxicity and serotonergic activity but limited studies examining long term outcomes

- VERY EXPENSIVE $$$$$

A 55 y/o woman presents with complaint of erythema, pain & warmth of her right lower leg for the past 3 days. Exam is consistent with non-purulent cellulitis

Which of the following would you prescribe?

A. Dicloxacillin
B. Cephalexin
C. Clindamycin
D. Doxycycline
E. Trimethoprim / Sulfamethoxazole

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B. Cephalexin
C. Clindamycin
D. Doxycycline
E. Trimethoprim / Sulfamethoxazole

A,B, and C are all technically correct. However, B is probably the BEST choice

Oral Penicillins

Penicillin VK, Dicloxacillin, Amoxicillin, Amoxicillin/clavulanic acid

Penicillin VK & Dicloxacillin

+	−
Non-purulent cellulitis	Optimal dose = every 6 hours → **Challenging for patients**

Amoxicillin

Spectrum of Activity

- *Strep* species
- *Enterococcus* species
- *H. influenza*
- *Moraxella catarrhalis*
- *E. coli*
- *K. pneumoniae*
- *Proteus mirabilis*

Common clinical uses

- Skin/soft tissue
- CAP
- GAS pharyngitis
- UTI

Amoxicillin/clavulanic acid (Augmentin)

Spectrum of Activity

- Same as amoxicillin
- + *Bacteroides*

Common clinical uses

- Skin/soft tissue
- Acute Sinusitis
- CAP
- Diverticulitis
- **Animal bites**

Adverse effects

- Diarrhea common! (10%)

Oral cephalosporins

1st: Cephalexin, cefadroxil
2nd: cefuroxime, cefaclor
3rd: cefdinir, cefpodoxime, cefixime

1st generation: cephalexin (Keflex), cefadroxil (Duricef)

Spectrum of Activity

- *Streptococcus* spp.
- MSSA
- *E. coli*
- *K. pneumoniae*
- *P. mirabilis*

Common clinical uses

- Skin & soft tissue infections (non-MRSA)
- Cystitis (BID dosing)
- *Do not use for serious infections

A 32 y/o woman presents for hospital follow up after her routine c-section is complicated by surgical site infection 10 days post-operatively. She was given IV vancomycin during admission & discharged with a course of cephalexin. She is breastfeeding and was instructed to "Pump & Dump".

Which do you recommend?

A. Continue to "Pump & Dump" until her body has cleared cephalexin based on half life
B. Discontinue the cephalexin because incision looks good
C. Start her on oral vancomycin instead
D. Reassure her the breast milk is safe & encourage her to return to direct feeds as this is a critical time in establishment breast feeding.

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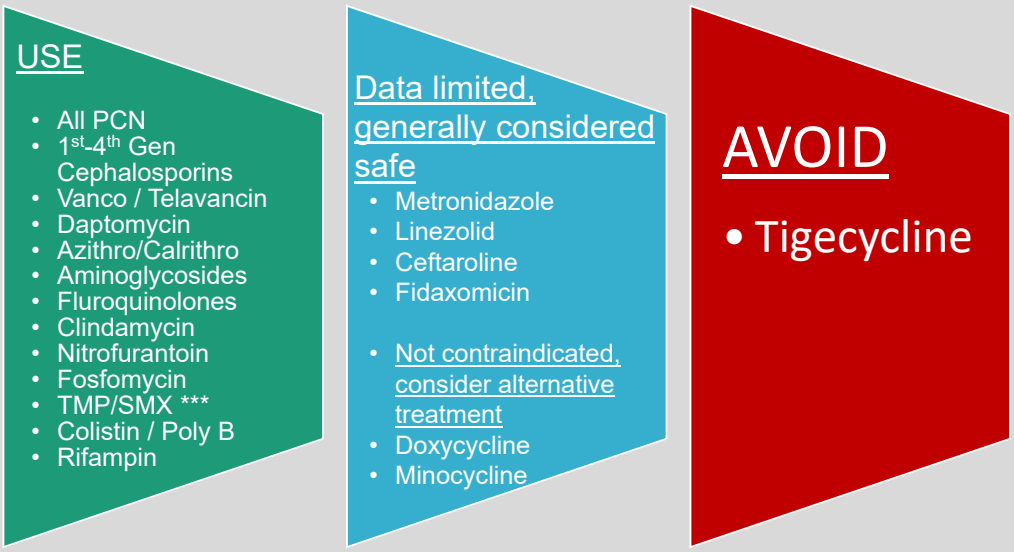
Which do you recommend?

Reassure her the breast milk is safe & encourage her to return to direct feeds as this is a critical time in establishment breast feeding.

Also – Education of your colleagues is imperative for future avoidance of this mistake. FYI - can anonymously ask Dr. Milk to send a letter to the provider as well.

Antibiotics & Breastfeeding



*** TMP/SMX - – Avoid in preterm infants or those with hyperbilirubinemia or G6PD deficiency. Generally safe when neonate is >1 month old

Antibiotics & Breastfeeding

- Try to do what is best for the patient & baby
  - → **Refrain from broadly recommending "Pump & Dump" on medication use in general**

- Good resources in general
  - LactMed (App no longer available)
  - For clinicians = InfantRisk App ($9.99)
  - Recommend For Parents = MommyMeds (Free!)

A 75 y/o woman with chronic urinary incontinence and chronic pelvic pain presents to her PCP for routine follow up. She was recently evaluated at an urgent care for a cough. A urine culture obtained noted growth of ESBL E coli.

Which antibiotic should you prescribe?

A. Send her to the hospital for IV ertapenem
B. Ciprofloxacin
C. Fosfomycin
D. Nitrofurantoin
E. Amoxicillin-clavulanate

A 75 y/o woman with chronic urinary incontinence and chronic pelvic pain presents to her PCP for routine follow up. She was recently evaluated at an urgent care for a cough and had a urine culture obtained with growth of ESBL E coli.

Which antibiotic should you prescribe?

A. Se[illegible]pital for IV ertapenem
B. [illegible]cin
C. [illegible]sfomyci[illegible]
D. N[illegible]furantoi[illegible]
E. Amoxi[illegible]vulanate

NONE!!!

She has Asymptomatic Bacteruria

A 43 y/o woman presents with new onset dysuria, increased urinary frequency and urgency. You appropriately prescribe her a course of cephalexin. However, her urine culture notes growth of ESBL E coli & she continues to have symptoms.

Which antibiotic should you prescribe?

A. Send her to the hospital for IV ertapenem
B. Ciprofloxacin
C. Fosfomycin
D. Nitrofurantoin
E. Amoxicillin + Clavulanate

A 45 y/o woman presents with new onset dysuria, increased urinary frequency and urgency. You appropriately prescribe her a course of cephalexin. Her urine culture notes growth of ESBL E coli & she continues to have symptoms.

Which antibiotic should you prescribe?

A. Send her to the hospital for IV ertapenem
B. Ciprofloxacin
C. Fosfomycin
D. Nitrofurantoin
E. Amoxicillin + Clavulanate

All answers are correct, but Nitrofurantoin is probably the **BEST** choice

UTI w/ ESBL Producing Bacteria
- Oral "Carbapenem Sparing" Antibiotics

- Fosfomycin
- Amoxicillin-clavulanate
- Nitrofurantoin
- Ciprofloxacin
- Trimethoprim - Sulfamethoxazole

Nitrofurantoin (*Macrobid*)

Nitrofurantoin – Pharmacology

- Well absorbed
- Appreciable concentrations in **urine** ONLY

Nitrofurantoin – Spectrum of Activity

- Most commonly used for
  - Enterobacterales (E coli, Klebsiella, etc)
  - Enterococcus (VRE)

Nitrofurantoin – Clinical use

- Cystitis!!!! [NOT pyelonephritis]
  - But ONLY if CrCl >50
- Duration for uncomplicated cystitis = 5 days
- Risk of pulmonary fibrosis / ILD in prolonged use
- DRESS syndrome: drug rash, eosinophilia & systemic symptoms

Fosfomycin

Fosfomycin - Pharmacology

- Not systemically absorbed (oral sachet)
- Renal elimination

Fosfomycin – Spectrum of activity

- MRSA
- VRE
- Enterobacterales (including **ESBL, KPC**)
- Pseudomonas aeruginosa (minimal)

Fosfomycin – Clinical use

- **UTIs with specific organisms**
  - **VRE, ESBL-producing organism and KPC-producing organism**

→ 3 gm oral dose x 1
  - May continue up to 21 days given every 3 days for complicated UTI
- Call lab for susceptibility testing
- May be challenging to find at pharmacy & can be expensive $$$

TMP/SMX - Clinical use

- SSTI
- **UTI**
- PCP prophylaxis

- Duration for uncomplicated cystitis is only **3 days**!

A 66 y/o man presents to your office with 5 days of profound diarrhea and abdominal pain. He was diagnosed with C diff colitis 4 months ago after a prolonged hospitalization for pneumonia & completed a 10 day course of oral vancomycin with resolution of symptoms. His C diff testing is + again.

Which do you recommend?

A. Oral metronidazole for 10 days
B. Oral fidaxomicin for 10 days
C. Oral vancomycin for 10 days
D. Hospital admission for IV vancomycin
E. Hospital admission for fecal transplant

A 66 y/o man presents to your office with 5 days of profound diarrhea and abdominal pain. He was diagnosed with C diff colitis 4 months ago after a prolonged hospitalization for pneumonia & completed a 10 day course of oral vancomycin with resolution of symptoms. His C diff testing is + again.

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B. Oral fidaxomicin for 10 days
C. Oral vancomycin for 10 days
D. Hospital admission for IV vancomycin
E. Hospital admission for fecal transplant

Could also consider a vanco taper afterwards

Fidaxomicin

Fidaxomicin– Clinical use

- **C diff colitis**!!!
  - Expensive $$$
  - Used primarily in setting of recurrence
    - Studies with decreased risk of recurrence
  - Dosing: oral 200 mg every 12 hours for 10 days

Metronidazole

Metronidazole - Pharmacology

- Rapid & almost completely absorbed
- Widely distributed
- Bactericidal

Metronidazole – Spectrum of Activity

- Gold standard for most Anaerobes
  - B. fragilis, Clostridium spp
  - Do NOT use for Actinomyces or Propionibacterium / Cutibacterium
- H. pylori
- Protozoa (Trichomonas, Giardia, Entamoeba)

Metronidazole – Clinical use

- **No longer used alone for C. diff colitis**
- **Still used for fulminant C diff with oral vancomycin**
- Intra-abdominal infections
- Trichomonas
- Bacterial vaginosis
- H. pylori

Metronidazole – Clinical use

<u>Note dosing for trichomonas vaginitis</u>

- Preferred regimen traditionally → metronidazole 2 g oral as a single dose
- Due to increasing resistance among women, recent studies suggest alternative regimen of **metronidazole 500 mg BID x 7 days** may be more effective

Metronidazole – Adverse effects

CNS toxicity

- Seizures, encephalopathy
- After 3 weeks: confusion & cerebellar dysfunction

Peripheral neuropathy

- when used for prolonged durations

GI side effects

- Nausea, diarrhea, metallic taste, "furry" tongue , dry mouth

Disulfiram- like reaction

- when combined with alcohol (N/V, flushing, tachycardia)

A 52 y/o woman with known aortic aneurysm is admitted to the hospital with fevers, productive cough, nausea/vomiting and headache. CXR concerning for multifocal PNA & Legionella urinary antigen returns positive.

Which antibiotic would you start?

A. Levofloxacin
B. Moxifloxacin
C. Azithromycin
D. Clarithromycin
E. Doxycycline

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B. Moxifloxacin
C. Azithromycin
D. Clarithromycin
E. Doxycycline

Macrolides

Erythromycin, Azithromycin, Clarithromycin

Macrolide - Pharmacology

- Well absorbed
- High tissue distribution
- Clarithromycin extensively metabolized by CYP450 (Inhibitor) = drug interactions

Macrolide spectrum of activity

Bacteria	Azithromycin	Clarithromycin
Atypicals	+	+
Strep pneumoniae	+/-	+
Strep pyogenes	+/-	+
M. catarrhalis, H. influenzae	+	
Toxoplasma gondii	+	+
Mycobacterium	+	+

Macrolide - Clinical use

Azithromycin	Clarithromycin
PCN allergic GAS pharyngitis	H. pylori
Atypical PNA coverage / CAP	MAC treatment / NTM
Chlamydia trachomatis	
Campylobacter enteritis	
?MAC prophylaxis	
NTM	

Macrolide – Adverse side effects

- GI intolerance
- Hepatic impairment
- QTc prolongation / ventricular tachycardia
- Metallic taste
- DRUG interactions --- Erythromycin & clarithromycin extensive list
  - Carbamazepine, cisapride, cyclosporine, digoxin, disopyramide, disulfiram, dofetilide, ergot alkaloids, lidocaine, loratadine, lovastatin, midazolam, pimozide, repaglinide, rifampin, rifabutin, ritonavir, saquinavir, simvastatin, sildenafil, tacrolimus, terfenadine, theophylline, verapamil, **warfarin**, zidovudine…. The list goes on
  - Thus would avoid using…

Lefamulin (Xenleta)

- FDA approved August 2019 for CAP treatment. (IV & oral options)
- FDA -Spectrum of activity: MSSA, Strep pneumoniae, H. influenza, Legionella, Mycoplasma pneumoniae & Chlamydophilia pneumoniae
  - But much broader coverage in reality: E faecium (including VRE), MRSA/VRSA, MDR S. pneumonia, fastidious gram negatives, oral anaerobes & atypicals
- Unclear if/how this drug will be utilized.

A 28 y/o person with injection drug use admitted for septic shock with MRSA triscupid valve endocarditis & pneumonia continues to have persistently positive blood cultures despite therapy with IV vancomycin

Which do you recommend?

A. Continue IV vancomycin
B. Stop vanco & start IV Daptomycin
C. Stop vanco & start IV linezolid
D. Stop vanco & start Daptomycin + linezolid
E. Stop vanco & start Daptomycin + ceftaroline

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MRSA Antibiotics

Oral
- TMP/SMX
- Doxycycline
- Clindamycin
- Linezolid
- Delafloxacin

Parenteral
- Vancomycin
- Daptomycin
- Ceftaroline
- Telavancin / ortiavancin/ dalbavancin
- Tigecycline
- Quinupristin / dalfopristin

Ceftaroline

- 5th generation cephalosporin & only with activity against MRSA
- Combines gram-negative activity of ceftriaxone + gram-positive activity of cefepime + MRSA
- NO Pseudomonas coverage
- Most hospitals likely require ID or ASP approval
- Primary role as salvage therapy for **refractory MRSA infections**

Daptomycin

- Similar spectrum of activity to vancomycin
- MRSA & VRE
- Cannot use for pneumonia
  - Cleaved by pulmonary surfactant
- Clinical use
  - Serious MRSA infections that “fail” or do not tolerate vancomycin
  - VRE

Daptomycin -Adverse effects

- Skeletal muscle toxicity
  - Recommend monitoring CK weekly
  - Usually appears have 7 days of therapy & resolves several days after stopping the drug
- Expensive $$$

Telavancin

- FDA approved in 2009
- Indicated for SSTI, HAP/VAP due to MRSA
- No VRE coverage
- IV only & dosed daily
- Continued issues with nephrotoxicity
- Rarely used clinically

Dalbavancin

- FDA approved in 2014
- Dosing- infusion now and additional infusion a week later
- Covers MRSA & VRE (+/- VanB)

- Expensive $$$

- Intended for long term MRSA treatment

Oritavancin

- FDA approved in 2014
- One infusion (takes 3 hours to infuse)
- Covers MRSA & VRE (both VanA & VanB)

- Expensive $$$

- Intended for long term MRSA treatment

A 42 y/o man with enterocutaneous fistula and multiple admissions for bacteremia due to line tampering is admitted in septic shock while completing a course of meropenem for ESBL Klebsiella & Pseudomonas bacteremia.

In addition to starting IV vancomycin, which antibiotic do you recommend?

A. Cefiderocol
B. Meropenem / vaborbactam
C. Eravacycline
D. Ceftolozane /tazobactam
E. Ceftazidime / avibactam

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Not enough information to appropriately answer this question…

Carbapenems

- Should be reserved for serious infections
  - ESBL coverage
  - Good anaerobe coverage
  - Some with Pseudomonas Coverage
  - Some with Acinetobacter coverage
  - Some coverage for Listeria
  - NO coverage of MRSA, Stenotrophomonas maltophilia or Enterococcus faecium

Carbapenems – clinical pearls

Ertapenem	Imipenem /cilastatin	Meropenem	Doripenem
ESBL Coverage	ESBL Coverage	ESBL Coverage	ESBL Coverage
NO Pseudomonas aeruginosa	+ Pseudomonas aeruginosa	+ Pseudomonas aeruginosa	+ Pseudomonas aeruginosa
	More side effects; especially seizures		Least likely to cause seizures
No coverage of Enterococcus or Acinetobacter	More data for treatment of **Nocardia** & **NTMs**		**NOT** recommended for HAP/VAP

Ambler Classification: Beta-Lactamases

Class	β-Lactamase Type	Host Organisms	Substrates
A	Extended-Spectrum (ESBL – TEM, SHV, **CTX-M**) Carbapenemases (**KPC**, GES, SME)	**Enterobacterales** Nonfermenters	Penicillins, Cephalosporins All **β**-lactams*
B	Metallo - carbapenemases (**IMP, VIM, NDM**)	Enterobacterales Nonfermenters	All **β**-lactams
C	AmpC - cephalosporinases (AmpC, CMY, ACT, ADC)	**SPACE/AMPCES**	Cephamycins 1st -3rd gen cephalosporins
D	Extended-Spectrum (OXA) Carbapenemases (OXA)	Enterobacterales **Nonfermenters**	Penicillins, Cephalosporins All **β**-lactams*

*Some **β**-lactamase inhibitors may remain effective

Ceftolozane / tazobactam (Zerbaxa)

- Ceftolozane is a new cephalosporin with enhanced activity against Pseudomonas aeruginosa
- Tazobactam enhances activity against beta-lactamases
- Activity against ESBLs and MDR P. aeruginosa
- FDA approved (2014) for complicated intraabdominal infections (w/ metronidazole), UTIs/pyelonephritis and HAP/VAP
- Reserved primarily for treatment of **MDR Pseudomonas** when alternative beta-lactams are non-susceptible

Ceftolozane / tazobactam (Zerbaxa)

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- FDA approved for complicated intra-abdominal infections (w/ metronidazole
- Reserved prim
when alternat

Currently, as of Dec 2020, voluntary recalled by Merck due to manufacturing issue related to sterility – recommended immediate discontinuation.

Ceftazidime / avibactam (Avycaz)

- Avibactam primarily restores activity for ESBL or AmpCs but restores some activity of ceftazidime to MDR Pseudomonas aeruginosa
- FDA approved (2015) for complicated intra-abdominal infections (w/ metronidazole), UTI/pyelonephritis, & HAP/VAP
- Primary therapeutic use generally for **Carbapenem resistant Enterobacterale**

Meropenem / vaborbactam (Vabormere)

- FDA approved in August 2017 for complicated UTI / pyelonephritis
- Activity against ESBLs and CREs
  - No activity against meropenem resistant Pseudomonas aeruginosa
  - Does not include MBLs or OXA-positive isolates

Iminipenem/ cilastatin / relebactam (Recarbrio)

- Relebactam restores imipenem activity for MDR Pseudomonas (very similar to avibactam)
- FDA approved in July 2019 for intraabdominal infections, complicated UTI / pyelonephritis & HAP/VAP
- Activity against CREs
  - Considered in Avycaz resistant CRE
- Retains some activity against MDR Pseudomonas aeruginosa
  - Considered in Zerbaxa-resistant PSA.

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Cefiderocol (Fetroja)

- "Trojan Horse" that utilizes siderophores transporting iron
- **The first cephalosporin stable in presence of metallo-beta-lactamases (MBLs) (**including CRE & NDM)
- Activity against Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia
- No activity against gram positive or anaerobic bacteria
- FDA approved for complicated UTI / pyelonephritis in November 2019.
  - More clinical data supports use in HAP/VAP and septic patients

Tetracycline

(Part 1)
Tetracyline, doxycycline, minocycline

(Part 2)
tigecycline
eravacyline, omadacycline

Tigecycline

- Expanded activity all around
- High volume distribution (low utility for bacteremia) and poor urinary excretion (limited used for UTI)
- Extensive side effects including N/V
- **Black box warning: Increased all-cause mortality (only use when no other option)**
- **Likely restricted at most hospitals**
  - **Consider use for XDR VRE or Acinetobacter spp**

Eravacycline

- FDA approved 2018; IV only
- Like tigecycline but 2-4x more potent against gram positive, 2-8x more potent against gram negatives
- Approved for intra-abdominal infections
- May not be available many institutions, clinical data still pending for Acinetobacter
- Place in therapy for **MDR Acinetobacter baumanii**

Omadacycline

- FDA approved in 2018, 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

Tetracycline Spectrum Overview

	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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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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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	++	++	++

New Agents Activity

Bacteria	Minocycline	Omadacycline	Eravacycline
ESBL producers	0	+	+++
KPCs	0	+	+++
Metallo-carbapen.	0	+	+++
Acinetobacter	Variable	++	+++
Stenotropho-monas	0	+	++

Aztreonam

- Spectrum of action – Gram negative coverage ONLY (including Pseudomonas aeruginosa)
- No coverage of gram-positive organisms OR anaerobes
- Safe with IgE mediated Penicillin/cephalosporin allergy & gram negative bacteria infection
  - Does have cross allergenicity with **ceftazidime**

Aztreonam

- Stable in presence of metallo-carbapenemases, however is inactivated by concomitant ESBL
  - Use of ceftazidime-avibactam PLUS Aztreonam to treat gram negative bacteria with co-producing ESBL & metallo-carbapenemase
- Otherwise, should probably be reserved for patients with **SEVERE Penicillin / cephalosporin allergies**

Comparison of new(er) Antimicrobials

Agent	β-Lactamases				Organisms		
	ESBL	KPC	OXA	MBL	CRE	*P. aeruginosa*	*A. baumannii*
Ceftolozane/ Tazobactam	+/-	–	–	–	–	+	–
Ceftazidime/ Avibactam	+	+	+/-	–	+	+/-	–
Meropenem/ Vaborbactam	+	+	–	–	+	–	–
Imipenem/ Relebactam	+	+	+/-	–	+	+	–
Eravacycline	+	+	+	+	+	–	+
Cefiderocol	+	+	+	+	+	+	+

Thank you