

Antibiotics Update
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- ### Goals
- Briefly discuss antibiotic overuse
 - Provide a clinical scenario followed by an 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

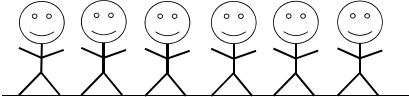
A collaborative response to combating antibiotic resistance & improve patient safety



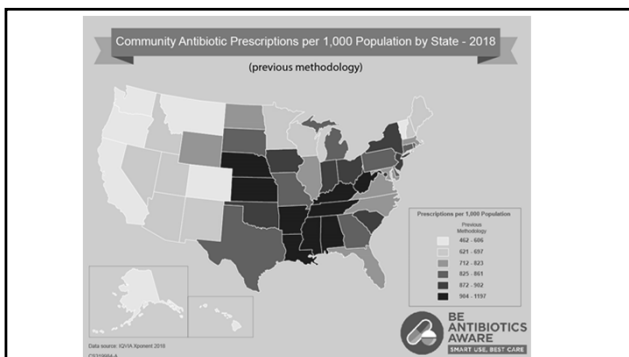
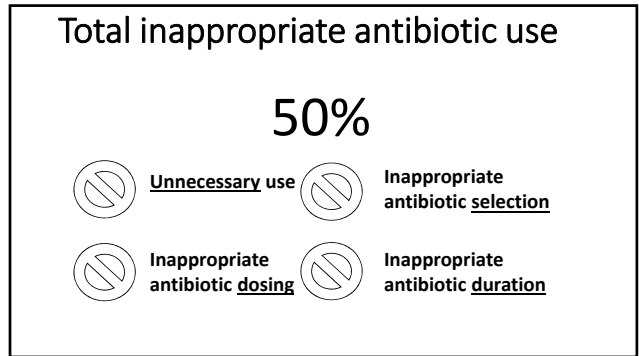
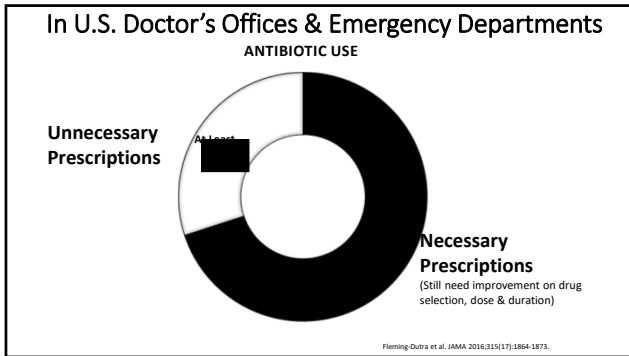
BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

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



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

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.

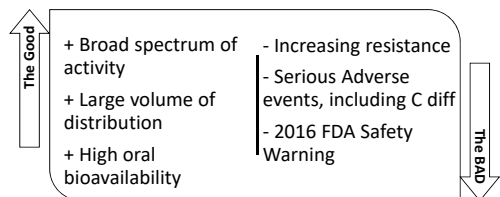
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- E. History of Achilles tendon injury

Fluoroquinolones

Ciprofloxacin, Levofloxacin,
Moxifloxacin, Delafloxacin

Fluoroquinolones (FQ)



→ **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 |
|------------------|---------------|--------------|--------------|-------------------|
| Enterobacterales | ++++ | +++ | +++ | +++ |
| 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 | <ul style="list-style-type: none"> • N/V • Abdominal discomfort • LFT abnormalities |
| CNS | <ul style="list-style-type: none"> • Headache • Dizziness • Insomnia • Delirium |
| CV | <ul style="list-style-type: none"> • QTc prolongation / Torsades • Aortic Aneurysm |
| MSK | <ul style="list-style-type: none"> • Arthropathy • Tendinitis / rupture |
| Derm | <ul style="list-style-type: none"> • 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?

- Clindamycin
- Doxycycline
- Trimethoprim-Sulfamethoxazole
- Cephalexin
- Linezolid
- Delafloxacin

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

MRSA Antibiotics

Oral

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

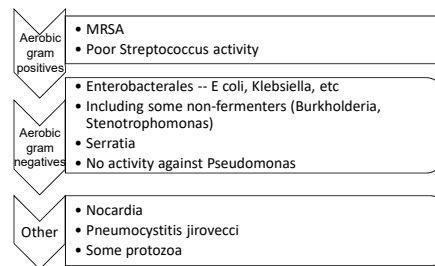
Parenteral

- Vancomycin
- Daptomycin
- Ceftaroline
- Telavancin / ortivancin/ 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)
Tetracycline, doxycycline, minocycline

(Part 2)
tigecycline
eravacycline, 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

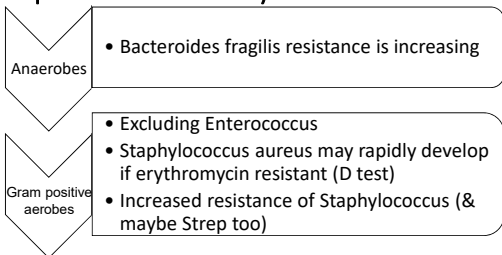
- Photosensitivity
- Pill esophagitis
 - avoid lying down for 30 minutes after dose
- Nausea/ vomiting
 - improved by taking w/ food
- Discoloration of teeth
 - Contraindicated in pregnancy & age < 8 years
- Nephrogenic diabetes insipidus
 - Demeclocycline (used for SIADH)

Clindamycin

Clindamycin - Pharmacology

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

Clindamycin – Spectrum of Activity



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

Hypersensitivity

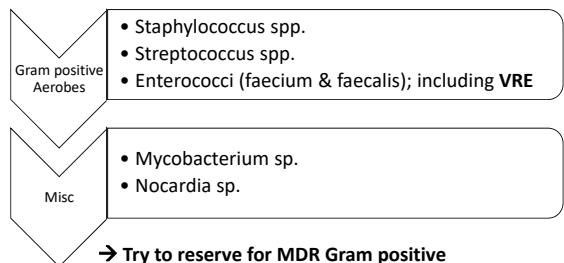
- Rash, drug fever, eosinophilia, anaphylaxis

Linezolid / Tedizolid

Linezolid– Pharmacology

- Great absorption, 100% bioavailable
- Great tissue penetration

Linezolid– Spectrum of Activity



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

The downsides

- 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?

- Dicloxacillin
- Cephalexin
- Clindamycin
- Doxycycline
- Trimethoprim / Sulfamethoxazole

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 cellulitis

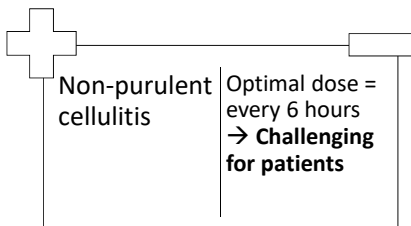
Which of the following would you prescribe?

- | | |
|------------------------------------|--|
| A. Dicloxacillin | A, B, and C are all technically correct. |
| B. Cephalexin | However, B is probably the BEST choice |
| C. Clindamycin | |
| D. Doxycycline | |
| E. Trimethoprim / Sulfamethoxazole | |

Oral Penicillins

Penicillin VK, Dicloxacillin, Amoxicillin, Amoxicillin/clavulanic acid

Penicillin VK & Dicloxacillin



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?

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

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?

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

| | | |
|--|---|---|
| <p><u>USE</u></p> <ul style="list-style-type: none"> • All PCN • 1st-4th Gen Cephalosporins • Vanco / Telavancin • Daptomycin • Azithro/Calithro • Aminoglycosides • Fluroquinolones • Clindamycin • Nitrofurantoin • Fosfomycin • TMP/SMX *** • Colistin / Poly B • Rifampin | <p><u>Data limited, generally considered safe</u></p> <ul style="list-style-type: none"> • Metronidazole • Linezolid • Ceftaroline • Fidaxomicin <p>• <u>Not contraindicated, consider alternative treatment</u></p> <ul style="list-style-type: none"> • Doxycycline • Minocycline | <p><u>AVOID</u></p> <ul style="list-style-type: none"> • Tigecycline |
|--|---|---|

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

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.

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
- 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

Note dosing for trichomonas vaginitis

- 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?

- Levofloxacin
- Moxifloxacin
- Azithromycin
- Clarithromycin
- Doxycycline

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

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 & Chlamydia 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 tricuspid 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

A 28 y/o injection drug user admitted for septic shock with MRSA tricuspid 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**

MRSA Antibiotics

Oral

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

Parenteral

- Vancomycin
- Daptomycin
- Ceftaroline
- Telavancin / ortivancin/ dalbavancin
- Tigecycline
- Quinupristin / dalbopristin

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 | Cepharmycins 1 st -3 rd gen cephalosporins |
| D | Extended-Spectrum (OXA) Carbapenemases (OXA) | Enterobacterales Nonfermenters | Penicillins, Cephalosporins All β -lactams* |

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

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Currently, as of Dec 2020, Zerbaxa was voluntarily recalled by Merck due to a 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 Enterobacterales**

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)
Tetracycline, doxycycline,
minocycline

(Part 2)

tigecycline
eravacycline, 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 baumannii***

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 | ++ | ++ | +++ | +++ | +++ |
| <i>S. pneumoniae</i> | +/- | +/- | +++ | +++ | +++ |
| <i>E. faecalis</i> | +/- | +/- | +++ | +++ | +++ |
| <i>E. faecium</i> , including VRE | +/- | +/- | +++ | +++ | +++ |
| <i>H. influenzae</i> , <i>M. catarrhalis</i> | ++ | ++ | +++ | +++ | +++ |
| <i>K. pneumoniae</i> and <i>E. coli</i> , including CRE and ESBL bla | +/- | +/- | ++ | + | +++ |
| <i>Enterobacter cloacae</i> | +/- | +/- | ++ | + | +++ |
| <i>Proteus</i> spp | 0 | 0 | 0 | 0 | +/- |
| <i>Pseudomonas aeruginosa</i> | 0 | 0 | 0 | 0 | 0 |
| <i>Acinetobacter</i> spp | 0 | ++ | ++ | ++ | +++ |
| <i>Stenotrophomonas malt.</i> | 0 | ++ | + | + | ++ |
| Atypicals | ++ | ++ | ++ | +++ | +++ |
| Anaerobes | 0 | 0 | ++ | ++ | ++ |

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| <i>Enterobacter cloacae</i> | +/- | +/- | ++ | + | +++ |
| <i>Proteus</i> spp | 0 | 0 | 0 | 0 | +/- |
| <i>Pseudomonas aeruginosa</i> | 0 | 0 | 0 | 0 | 0 |
| <i>Acinetobacter</i> spp | 0 | ++ | ++ | ++ | +++ |
| <i>Stenotrophomonas malt.</i> | 0 | ++ | + | + | ++ |
| Atypicals | ++ | ++ | ++ | +++ | +++ |
| Anaerobes | 0 | 0 | ++ | ++ | ++ |

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|--|-------------|-------------|-------------|--------------|--------------|
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| <i>Enterobacter cloacae</i> | +/- | +/- | ++ | + | +++ |
| <i>Proteus</i> spp | 0 | 0 | 0 | 0 | +/- |
| <i>Pseudomonas aeruginosa</i> | 0 | 0 | 0 | 0 | 0 |
| <i>Acinetobacter</i> spp | 0 | ++ | ++ | ++ | +++ |
| <i>Stenotrophomonas malt.</i> | 0 | ++ | + | + | ++ |
| Atypicals | ++ | ++ | ++ | +++ | +++ |
| Anaerobes | 0 | 0 | ++ | ++ | ++ |

New Agents Activity

| Bacteria | Minocycline | Omadacycline | Eravacycline |
|--------------------------|-------------|--------------|--------------|
| ESBL producers | 0 | + | +++ |
| KPCs | 0 | + | +++ |
| Metallo-carbapen. | 0 | + | +++ |
| <i>Acinetobacter</i> | Variable | ++ | +++ |
| <i>Stenotropho-monas</i> | 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 | <i>P. aeruginosa</i> | <i>A. baumannii</i> |
| Ceftolozane/ Tazobactam | +/- | - | - | - | - | + | - |
| Ceftazidime/ Avibactam | + | + | +/- | - | + | +/- | - |
| Meropenem/ Vaborbactam | + | + | - | - | + | - | - |
| Imipenem/ Relebactam | + | + | +/- | - | + | + | - |
| Eravacycline | + | + | + | + | + | - | + |
| Cefiderocol | + | + | + | + | + | + | + |

Thank you

