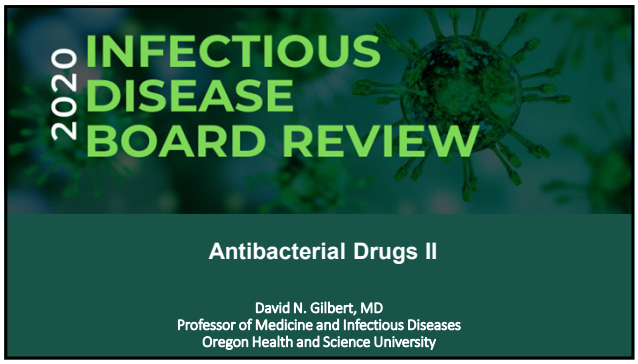
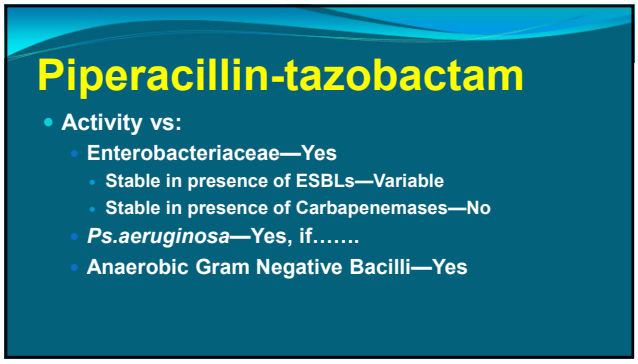
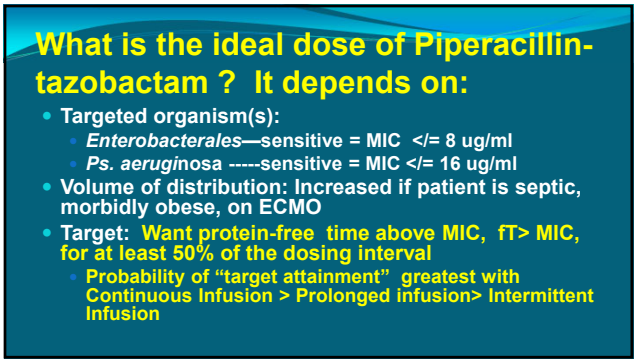
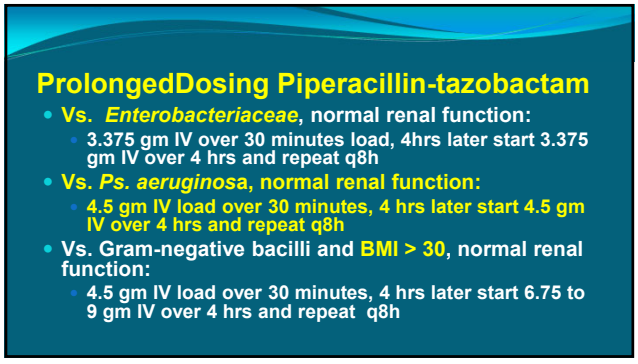
61 – Antibacterial Drugs II

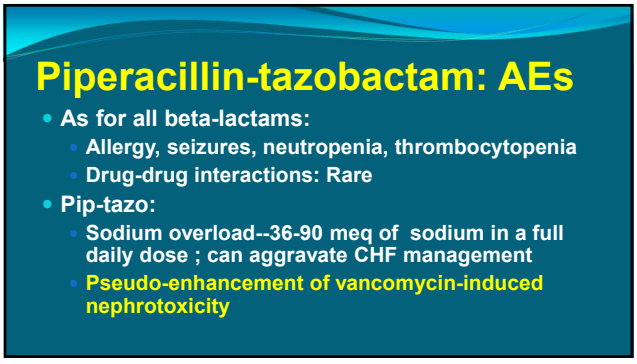
Speaker: David Gilbert, MD











Etiology of elevated Creatinine with Combination of P/T and Vancomycin

- RIFLE and KDIGO markers of AKI use serum creatinine as a surrogate for the GFR
- Creatinine is filtered by glomeruli and secreted by the renal tubules
- Known since 1980s that piperacillin competes with creatinine for tubular secretion
  - Shown in animals and humans
  - Increase in Creatinine does not reflect injured tubules
- Hence, elevation of the serum creatinine is expected
  - Similar to creatinine secretion blockade by trimethoprim, cimetidine, and selected antiretrovirals

* J. Clin Med 2019;8:781; J Antibiotics 1986; 39: 699; JAC 1994;34:555

Summary: Vanco:P/T as of 2020

- Vancomycin is potentially nephrotoxic
- Piperacillin-tazobactam alone has a very low potential to cause nephrotoxicity
- The reported increased ACUTE KIDNEY INJURY with V + P/T is at least partly due to the blockade of the renal tubular secretion of creatinine by piperacillin
- Current evidence would suggest that the combination of V+P/T is no more nephrotoxic than Vancomycin alone

Ampicillin-Sulbactam

- Activity vs.:
  - Enterobacterales—Yes, but decreasing
  - *Acinetobacter*—Sulbactam component yes (need high dose) and combination therapy
  - Anaerobic GNBs— Activity Equivalent to Pip/tazo
- Dose for sulbactam component for Acinetobacter* : 4 hr IV infusion of 9 gm of Amp-Sulb (6 gm Amp +3 gm Sulb) q8h

European J of Pharm. Sci. 2019; 136:104940

Cephalosporin "Generations"

Generation	Spectrum	Comment
First (Cefazolin)	*MSSA; E.coli, Kleb.sp.*	No activity versus enterococci
Second(Cefoxitin, Cefotetan)	Originally *Bacteroides fragilis*	*B.fragilis* resistance increasing
Third(Ceftriaxone[ctx])	Most of the aerobic GNBs: Enterobacterales	"Extended spectrum"
Fourth (Ceftazidime; Cefepime)	Antipseudomonal	Cefepime not porin dependent
Fifth (Ceftaroline)	Like CTX + MRSA	No act. enterococci
Sixth (Ceftolozane/Tazo)	ESBL producing GNBs	No activ. Vs. Bacteroides species
Seventh (Ceftaz/Avibactam)	(ESBL producing GNBs) & KPCs	Inconsistent activity vs Bacteroides

Cephalosporin "Generations"

Generation	Spectrum	Comment
Eighth: Cefiderocol	Metallo-Carbapenemase produced by Enterobacterales and Non-fermenters*	No activity vs Gram positives and anaerobic bacteria

* Non-fermenters: *Ps.aeruginosa, A. baumannii, Stenotrophomonas maltophila*

To survive bacteria are constantly mutating

- More than 2800 beta-lactamases reported
- Promiscuity among bacteria is rampant
- Not unusual to have additional mechanisms of resistance: e.g.,
  - Target change
  - Active efflux pumps
  - Decrease in permeability
  - Mechanisms of "R" not defined by phenotypic suscept. testing
- IF patient fails clinically and/or failure to eradicate pathogen, strongly consider whole genome sequencing
- NO surprise, hard to create "resistance " test questions

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Ambler Molecular Classificaton of Beta-Lactamases*

Class	Subtypes	Inhibitor ??	Substrates
A	ESBLs KPCs;serine carbapenemases	Clavulanic Avibactam & Vaborbactam	ESCs Carbapenems
B (BAD!)	Metallo-carbapenemases	EDTA(lab testing only)	All beta-lactams except aztreonam & Cefiderocol
C	AmpC	None	Cephalosporins
D	Oxacillinase-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	None Clavulanic Avibactam & Vaborbactam	Penicillins, Carbapenems, ESCs, & Aztreonam ESCs and Carbapenems

*Ambler: Based on nucleotide sequencing

Ceftriaxone "R" Enterobacterales

- 25% "R" of organisms in the order Enterobacterale worldwide; In Asia, 50% of *E.coli* are CTX resistant
- Most common mechanism of resistance:
  - Production of Extended spectrum beta-lactamases (ESBLs)
    - Phenothypic Dx: In vitro "R" to ceftriaxone and aztreonam; Lower MIC with clavulanic acid
  - If *Enterobacter species detected*: Production of Amp C cephalosporinases is the major concern
  - Carbapenems effective in presence of both ESBLs and AmpC enzymes
    - Are there any "carbapenem sparing" cephalosporins for ESBLs ?

MERINO Trial: P/T vs Mero for *E.coli*, *K.pneumoniae* ESBL Producers

- Design: PRDB.* 72 hrs from pos.culture to enroll; 30 minute infusions
- Endpoint: 30 day all cause mortality:
  - Piperacillin-tazobactam: 12.3 %
  - Meropenem: 3.7 %
- Issues:
  - Breakpoints/inoculum effect for P/T
  - Co-production of ESBL and oxacillinase
- Three confirmatory controlled trials in progress

* PRDB=Prospective Randomized Double-Blind

Collateral Damage from Carbapenem Therapy

- Selection of Carbapenem "R" strains of Enterobacterales, and/or Non-Fermenters (e.g., *Stenotrophomonas*)
- Selection of vanco "R" enterococci, MRSA, Candida species
- Nonetheless, based on the MERINO trial, Meropenem is Drug of Choice for treatement of ESBL producing *Enterobacterales*

Carbapenem Sparing Cephalosporins Active vs GNB producing ESBLs and/or AmpC

Cephalosporin active Vs:		
	AmpC producers	ESBL producers
Ceftazidime	Variable	Variable
Cefepime	If low MIC ; Big dose	If low MIC; Big dose
Ceftolozane-tazobactam	YES	YES
Ceftazidime-avibactam	YES (OK; $$$$$)	YES (OK; $$$$$)
Cefiderocol	YES (BIG OK; $$$$$)	Yes (BIG OK; $$$$$)

OK = OVERKILL

Reference: Curr Opin Infect Dis 2020;33: 78

Oral "Carbapenem-Sparing" Antibiotics for ESBL Producing Bacteria Causing UTI

- **F**osfomycin
- **A**moxicillin-clavulanate
- **N**itrofurantoin

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Testable Cephalosporin AEs

- Allergy: Ceftazidime and Aztreonam have same side chain
- Ceftriaxone: Pseudo-cholelithiasis
- Cefepime: Non-convulsive status epilepticus
- No Drug-Drug interactions

Carbapenems: Spectrum

Active versus:	NOT ACTIVE versus
Enterobacterales +/- ESBLs	*MRSA*
*Pseudomonas aeruginosa**	*Stenotrophomonas maltophila*
Bacteroides fragilis	
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	*Acinetobacter (variable)*

*Resistance can emerge during therapy via porin closure and efflux pumps or acquisition of carbapenemase

Carbapenem Family

Carbapenem	Comment(s)
Imipenem-cilastatin	Avoid in meningitis patients: seizure potential
Meropenem	Less potential for inducing seizures
Ertapenem	Not active vs *Ps.aeruginosa*; Once daily therapy
Doripenem	↑mortality vs Imipenem in VAP trial
Meropenem-vaborbactam and Imipenem-cilastatin-relebactam	Active vs *Klebsiella* producing carbapenemases (KPCs); Not active vs metallo or Oxa 48 carbapenemases

FDA Approved Beta-Lactam Beta-Lactamase Inhibitor Combinations

Penicillins	Cephalosporins	Carbapenems
Amoxicillin-clavulanate	Ceftolozane-tazobactam	Meropenem-vaborbactam
Ampicillin –sulbactam	Ceftazidime-avibactam*	Imipenem-cilastatin-relebactam
Piperacillin-tazobactam		

Note: so far 6 Beta-lactam inhibitors and none inhibit class B metallo-carbapenemases

* Only avibactam inhibits chromosomally-mediated AmpC ESBLs

The Major Families of Carbapenemases

Non-Metallo (Serine at active site)	Metallo (Zinc at active site): VIN
KPC (Class A)	VIM (Class B)
OXA-48 et al (Class D)	IMP (Class B)
	New Dehli Metallo- Blasé (Class B)

KPC=Klebsiella-producing carbapenemases; OXA=oxacillinase; IMP=Imipenemase; VIM=Verona integron-encoded metallo Blamase; NDM= New Dehli metallo

Ambler Classification of Beta-Lactamases

Ambler Group	A	B	C	D
Binding Site	Serine	Metallo	Serine	Serine
Enzymes	ESBLs;KPCs	Carbapen-ase	Cephalo-ase	Oxacil—ase/Carba
TREATMENT:				
Ceftaz.-avi*	+	---	+	+(Oxa-48)
Mero-vabor*	+	---	+	---
Imi-relebact	+	---	+	---
Ceftaz-avi+AZ	+	+	+	+
Cefepime	---	---	---	+(Oxa)
Cefiderocol	+	+	+	+

*Active vs Ceftaz-avi resistant KPCs

ARQ #1

- 60 y.o. female smoker, admitted, intubated, and ventilated due to severe COPD with Acute Respiratory Failure.
- Chest X-Ray: New bibasilar infiltrates and Emphysema
- Empiric ceftriaxone and azithromycin
- Sputum positive for both rhinovirus and ***Klebsiella pneumoniae*** resistant to both ceftriaxone and azithromycin
- Also "R" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems

ARQ #1

- Which one of the following antibiotics would you select for this KPC infection ?
  - A. Tigecycline
  - B. Ceftazidime-avibactam
  - C. Aztreonam
  - D. Ceftolozane-tazobactam

Treatment of Carbapenem Resistant Enterobacteriaceae (CRE)

- *Klebsiella (or E. coli)* producing carbapenemase (KPC) most common
- Serine based as opposed to metallo-carbapenemase
- Serine Enyzme activity blocked by avibactam and vaborbactam; hence protects activity of : Ceftazidime-avibactam and Meropenem-vaborbactam
- Concomitant ESBLs inactivate aztreonam
- Tigecycline failures in pneumonia patients
- Ceftolozane-tazobactam is stable in presence of ESBLs but is hydrolyzed by KPCs

Beta-Lactam Treatment of Carbapenemase Producing GNBs

- Class A (KPCs-Klebsiella-Producing Carbapenemases):
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam; Imipenem-cilastatin-relebactam
  - Cefiderocol
- Class B (Metallo-carbapenemases):
  - Ceftazidime-avibactam + Aztreonam
  - Cefiderocol
- Class C(cephalosporinases): Carbapenem
- Class D (OXA-type) carbapenemases (heterogeneous and low level enzymatic hydrolysis)
  - May be susceptible to ceftazidime and cefepime.
  - Ceftazidime –avibactam. Interest in combination therapy.
  - Not currently testable!

AZTREONAM (monobactam)

- Only beta-lactam with NO activity vs. Gram positive bacteria: e.g., *S. pneumoniae !!!!!!!!!*
- Safe with IgE mediated Pen/Ceph.allergy & aerobic GNB infection; cross allergenicity with ceftazidime
- In vitro resistance of GNB to aztreonam is a phenotypic marker for production of ESBLamases
- Stable in presence of metallo-carbapenemases; however, inactivated by concomitant ESBLs
- Use Ceftazidime-avibactam plus aztreonam to treat GNB co-producing ESBL and metallo-Carbapenemase

Aztreonam and Carbapenemases

Active versus:	NOT active versus:
Metallo-Carbapenemases (Gp B)	Klebsiella-producing Carbapenemases (KPCs)(Gps A & D)
Enterobacterales(if no ESBLs)	ESBL producers
Pseudomonas aeruginosa	*Acinetobacter; Stenotrophomonas*

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Cefiderocol

- First cephalosporin stable in presence of GNB producing metallo-beta-lactamases
- "For complicated UTI due to susceptible GNB with no other treatment options"
- Spectrum of activity:
  - XDR Enterobacterales
  - XDR Non-fermenters (Steno, Pseudo, Acineto)
  - No activity vs gram + bacteria or anaerobic bacteria

Cefiderocol

- Clinical studies:
  - Microbial eradication: Imipenem 56% ; Cefiderocol 73%
  - Day 14 mortality: Best available therapy 12 %; Cefiderochol 25%
- Has catechol side chain that utilizes iron transport system (siderophore). "Trojan horse"
- No serious AE , so far: GI 2-4%, C.difficile, Seizures
- For salvage therapy when no other option available

Fluoroquinolones

Finally, beyond beta-lactams.

Fluoroquinolones (FQs)

- Family: Ciprofloxacin, Levofloxacin, Moxifloxacin, Delafloxacin
- The GOOD: Broad Spectrum of Activity, Large volume of distribution, High oral bioavailability
- The BAD: Increasing "R", Serious AEs(C.diff.) Many Drug-Drug interactions; 2016 FDA Safety Warning.
- Conclusions:
  - Uncomplicated infections(bronchitis)---AVOID
  - Severe infections---RISK vs Benefit

FQ Selected Activity(0-4+)

Bacteria	Ciprofloxacin: BID	Levofloxacin: Once daily	Moxifloxacin: Once daily	Delafloxacin: Once daily
Enterobacterale	4+	3+	3+	3+
Ps.aeruginosa	4+	2+	0	2+
Acineto; Steno	0	0	0	?
MRSA	0	0	0	4+(20% "R"
Anaerobes	0	0	4+	2+
Mycobacteria	0	4+	4+	0
Anthrax;*Sal.typhi*	4+	4+	4+	4+

Resistance ("R") to FQs

- Antibacterial due to blockade of DNA replication via binding to DNA Gyrase and Topoisomerase enzymes
- Multiple mech. Of "R":
  - Mutations of enzyme targets
  - Efflux pumps, altered cell wall permeation
  - Target protective proteins, drug acetylation
- Concomitant "R" of GNB to beta-lactams via:
  - Production of ESBLs
  - Production of Carbapenemases

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FQ Pharmacology

- Parenteral:
  - Higher doses for *Ps.aeruginoa*
  - Excreted in urine
  - High concentrations in prostate
- Oral:
  - Bioavailability of 59-95%
  - Chelation by divalent cations decreasing bioavailibility:
    - Calcium
    - Iron
    - Zinc, Magnesium, Aluminum

FQ Adverse Events

- *Clostridioides difficle* (the leader) colitis
- Neurologic
  - Confusion, delirium, seizures (GABA blockade)
  - Peripheral neuropathy
  - Exacerbate myasthenia gravis
- Cardiovascular
  - Prolongation of QTc !!!
  - Aortic aneurysm and dissection
- Tendonopathy/Arthropathy
- Dysglycemic

QTc Prolongation: Potential Risk with all FQs except Delafloxacin

- >500 msec. or > 60 msec prolongation from baseline increases risk of torsades de pointes & ventricular fibrillation.
- Low serum K and/or Mg ; Concomitant drugs increase risk: e.g., mefloquine, haldol, fosphenytoin.
- None of FQs are high risk used alone; problem: concomitant drugs (cytochrome P-450 inhibition), electrolyte abnormalities.

Tetracyclines: The Family

- Doxycyline (Many indications)
- Minocycline(Many indications)
- Tigecycline (Don't use)
- Omadacycline(SSTIs, CABP)
- Eravacycline (cIAIs)

Tetracycline Activity Spectrum

Bacteria	Doxycycline	Minocycline	Omadacycline	Eravacycline
Aerobic GPCs	+	+	+	+
MRSA	+	+	+	+
Aerobic GNB	+	+	+	+
Rickettsial	+	+	+	+
Spirochetal*	+	+	+	+
Plasmodia	+	?	?	?
Ps.aeruginosa	0	0	0	0
Acineto/Steno.	0	Variable	+	+

*Borrelia, Treponema, Leptospira

Tetracyclines: Mechanism & "R"

- Antibacterial Mechanism:
  - Binds 30S ribosome, inhibits protein synthesis, Bacteriostatic
- Mechanisms of Resistance:
  - Reduced permeability and/or increased efflux
  - Blockade of ribosome binding site by protection proteins

Tetracycline Pharmacology

- Oral absorption impaired by multivalent cations
- Distribution largest with minocycline (greatest lipid solubility)
- Distribution and Tigecycline:
  - High intracellular levels; very low extracellular concentrations
  - FDA review found increased mortality
  - "Only use when no other option"
- Avoid in pregnancy and children < 8 y.o.

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Tetracycline Adverse Effects

- *Clostridioides difficile* colitis
- Photosensitivity
- Hepatotoxicity: minocycline; pregnancy
- Nephrogenic diabetes insipidus due to demeclocycline (for SIADH)
- Spirochetal infections and Jarisch-Herxheimer reactions
- Vertigo: Minocycline

Tetracyclines: In Vitro Activity versus MDR GNB

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

Aminoglycoside Family

- Amikacin
- Gentamicin
- Streptomycin
- Plazomicin
- Tobramycin

AG: Spectrum of Activity

- Active vs.:
  - Aerobic gram-negative bacteria
  - Typical and atypical mycobacteria
  - Variable: *Ps.aeruginosa, S. aureus* X 24 hrs
- No activity vs.:
  - Gram-positive cocci: e.g., *S.pneumoniae*
  - Anaerobic bacteria
  - Non-fermenters: *Acinetobacter sp., Stenotrophomonas maltophilia*
- Often part of combination therapy

AG: Mech. of Action & "R"

- Binds to 30s ribosome; Concentration-dependent Bactericidal activity
- Multiple mechanisms of resistance:
  - Most Frequent
    - Enzymatic alteration of drug: adenyl., acetyl., phosporyl.
      - Plazomicin not susceptible to enzymatic attack
    - Methylation of ribosomal binding site
  - Less Common
    - Efflux pump
    - Porin closure
- Bacteria "R" to beta-lactams often have concomitant "R" to AGs

AG: Pharmacology

- Basis of once daily dosing:
  - Concentration dependent cidal activity
  - Long post-antibiotic effect
- Result is improved antibacterial activity and less risk of toxicity
- EXCEPTION: Combination therapy of enterococcal endocarditis

AG: Shared Adverse Effects

- Nephrotoxicity: Acute tubular necrosis
- Ototoxicity:
  - Cochlear (genetic predisposition & non-reversible)
  - Vestibular (irreversible but host can compensate)
- Neuromuscular blockade (neomycin)

Polymyxin Family

- Polymyxin B
- Polymyxin E (Colistin)

Polymyxins: Mechanisms of "R"

- Mechanism:
  - Binds to LPS & Phospholipids of cell wall of GNB
  - Displaces divalent cations; resulting membrane disruption, and bactericidal activity
- Resistance is increasing, esp. Carbapenemase producing GNBs
  - Due to LPS target change and efflux pumps
  - Plasmid spread of mcr-1 gene
- Guideline reference: Pharmacotherapy 2019;39: 10

Activity vs Aerobic GNB

- Susceptible: *Enterobacterales, ESBLs, KPCs, non-fermenters (Acinetobact., Stenotroph., Ps. Aeruginosa*
- Intrinsic Resistance: M—*Moraxella*
  - *a----a vowel*
  - *P---Proteus*
  - *P---Providencia*
  - *S---Serratia*
- All gram + bacteria are "R"

Polymyxin Pharmacology

- Polymyxin B
  - Uncomplicated dosing
  - Non-renal clearance
  - Drug of choice except for UTI
- Colistin (pro-drug)
  - Complicated dosing
  - Renal excretion
    - Use for UTIs
    - Adjust dose for renal insufficiency
- Often used as part of combination therapy

Polymyxins: Adverse Effects

- Nephrotoxicity. Lower risk with polymyxin B
- Neurotoxicity. Wide range of problems:
  - Dizziness
  - Paresthesias
  - Vertigo
  - Confusion
  - Ataxia
  - Neuromuscular blockade

Trimethoprim-Sulfamethoxazole

- Mechanism of action:
  - Sequential blockade of two enzymes needed to synthesize folate
- Broad spectrum---Activity vs. GNB:
  - Enterobacterales
  - Non-Fermentative GNBs: *Burkholderia and Stenotrophomonas.*
    - *No activity vs Ps.aeruginosa*
    - Also , no activity vs:*Mycoplasma, Francisella tularensis, and Bacteroides fragilis*

TMP/SMX: Pharmacology

- Widely distributed to include CSF and Prostate
- Renal excretion by both tubular secretion and glomerular filtration
- Lots of Drug-Drug interactions

TMP/SMX: Adverse Effects

- Hyperkalemia due to TMP and /or ACEIs/ARB due to interference with tubular secretion
- Neutropenia
- Promotes folate deficiency; Dangerous in pregnancy----neural tube defects
- Derm.: Stevens Johnson syndrome; toxic epidermal necrolysis
- Aseptic meningitis

Nitrofurantoin for uncomplicated *E.coli* UTI*

- Pulmonary toxicity with chronic therapy: desquamative interstitial pneumonia with fibrosis
- Intrahepatic cholestasis and hepatitis
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

*Cystitis only

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Metronidazole

- Antibacterial and anti-protozoan activity requires a strict anaerobic environment
- "Gold Standard" for treatment of *Bacteroides species*
  - Other Drugs active vs *B.fragilis*: Pip/tazo, Amp/sulb, and Carbapenems
- Other clinical Indications: Bacterial vaginosis, Amebiasis, Giardiasis, and *Trichomonas vaginitis*
- Metro. "R" Anaerobes: *P. (Cutibacterium) acnes, Peptostreptococci, Eikenella* and *Actinomyces*

Metronidazole: Adverse Effects

- Metallic taste; "furry" tongue
- Disulfiram reaction (N/V, flushing, tachycardia, dyspnea) after alcohol
- Prolonged use: peripheral, autonomic , and/or optic neuropathy
- Aseptic meningitis
- After 3 weeks: confusion and cerebellar dysfunction

Is the patient's encepalopathy due to your antibiotic therapy ?

Antibiotic	Time to onset	Syndrome
Beta-Lactams	Within days *	Seizures; abnormal EEG
FQs, Macrolides	Within days	Delusions/Hallucinations; normal MRI
Metronidazole	Weeks	Cerebellar dysfunction with abnormal MRI

* High serum concentrations due to renal insufficiency

Reference: Neurology 2016; 86:963