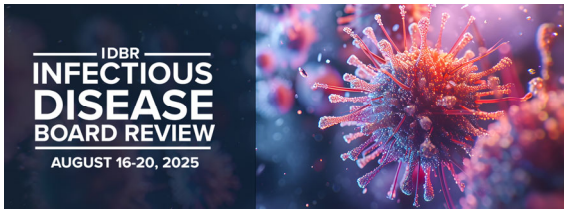

Antimicrobial Drugs Not Covered Elsewhere: 10 Issues You Might Get Asked About

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6/11/2025

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Disclosures of Financial Relationships with Relevant Commercial Interests:

- Contributing Editor, *The Sanford Guide to Antimicrobial Therapy*

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Case #1

- A 22-yo woman presets with acute onset chest pain and painful swallowing
- Onset: 2 days ago
- Sharp retrosternal chest pain worsened by swallowing
- No history of reflux or GERD. No fever, cough, or SOB
- UGI endoscopy: Linear ulcerations in mid-esophagus, mucosal erythema, superficial erosions
- Recently began a new antibacterial medication for a skin condition five days ago
- Dx: drug-induced (pill) esophagitis

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Question #1

Based on the case, which antibacterial do you suspect she was taking?

A. Levofloxacin
B. Cephalexin
C. Linezolid
D. Metronidazole
E. Doxycycline

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Pill Esophagitis

- Inflammation or ulceration of the esophageal mucosa caused by direct contact with a drug.
- Symptoms appear hours (even days) after drug ingestion
- Antimicrobial offenders: Tetracyclines, penicillins, TMP-SMX, clindamycin, spiramycin, erythromycin, rifampin, tinidazole, AZT, azithromycin
- Risk factors:
  - Supine position after drug ingestion
  - Inadequate water intake
  - Pre-existing esophageal motility disorders or strictures
  - Older age
  - Large or multiple medications
- Management
  - Discontinue offending agent
  - Sucralfate, PPIs, viscous lidocaine
  - Hydration, soft diet

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Case #2

- A 76-yo woman presents with acute confusion, hallucinations and tremors that began two days ago.
- PMH: hypertension, hyperlipidemia, CKD (CrCl ≈40 mL/min).
- VS: BP 138/78, HR 84, afebrile.
- Home meds: metoprolol, hydrochlorothiazide, amlodipine, rosuvastatin.
- Head CT: No acute abnormalities. LP: no pleocytosis, glucose and protein are within normal limits.
- Four days ago, began valacyclovir 1 gm q8h for shingles.

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Question #2

Which of the following is a risk factor for valacyclovir neurotoxicity in this patient?

A. Renal impairment
B. Treatment with hydrochlorothiazide
C. Hyperlipidemia
D. Hypertension
E. Active VZV infection

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Valacyclovir Neurologic Toxicity

- Presentation
  - Early: agitation, hallucinations, confusion, disorientation
  - Later: tremor, myoclonus, delirium
  - Rare: seizures, extrapyramidal symptoms
- Key risk factors
  - Renal impairment
  - Age
  - High doses
  - Dehydration
- Pathophysiology: accumulation of CMMG (9-carboxymethoxymethylguanine)
- Management
  - Stop drug
  - Adjust dosage if therapy must be continued
  - Hydration
  - Hemodialysis in extreme cases

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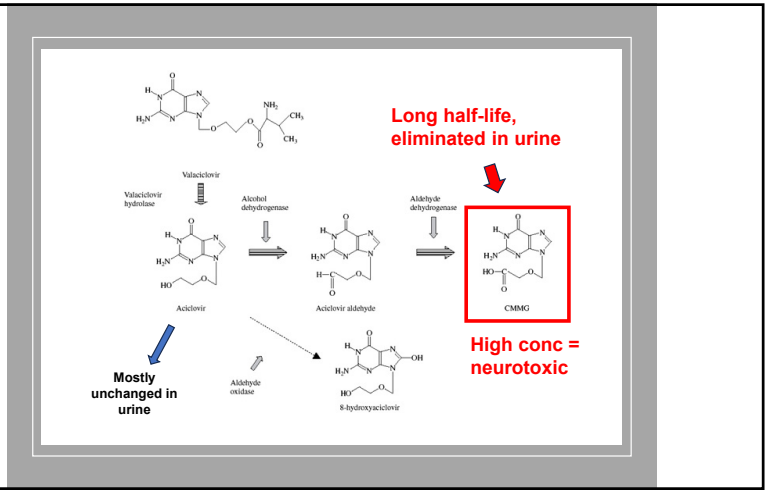

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Case #3

- A 9-month-old male infant is brought to the pediatric clinic by his parents due to increased fussiness, poor sleep, and decreased appetite over the past 48 hours. He has been tugging at his right ear.
- He has a low-grade fever (38.3°C) and rhinorrhea. No vomiting or diarrhea.
- ENT exam: Bulging, erythematous right tympanic membrane with reduced mobility on pneumatic otoscopy, mild nasal congestion.
- The family reports difficulty administering liquid amoxicillin in the past due to taste, and they prefer a once-daily dosing option. Cefdinir 14 mg/kg q24h x10 days is chosen.

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Question #3

What adverse effect specific to cefdinir should the parents be warned about?

A. Serum sickness
B. Brown urine
C. Red stools
D. Skin discoloration
E. Nausea

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Cefdinir-associated Red Stools

- Red or reddish-orange stools occurring in infants and young children. May be interpreted as "bloody diarrhea."
- Cause: cefdinir + iron-fortified infant formula or supplements → non-absorbed complex → red stool
- NOT due to GI bleeding. No abdominal pain or other GI symptoms.
- Typically appears within 1-5 days of starting therapy.
- Can continue the drug, or switch to something else.
- Parent counseling
  - Harmless discoloration
  - Cefdinir therapy should continue
  - Resolves after stopping iron or drug

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First generation
- Cefazolin
- Oral: cephalexin, cefadroxil

Second generation
- Cefotetan, cefoxitin, cefuroxime
- Oral: cefaclor, cefprozil, cefuroxime axetil

Third generation
- Ceftriaxone, cefotaxime
- Ceftazidime
- Oral: cefpodoxime proxetil, cefdinir, cefixime

Fourth generation
- Cefepime

Fifth generation (covers MRSA)
- Ceftaroline

Others (don't fit well into "generations")
- Cefepime-enmetazobactam, cefiderocol, ceftazidime-avibactam, ceftobiprole, ceftolozane-tazobactam

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Case #4

- 62-yo man presents with a 3-week history of worsening pain, swelling, and foul-smelling discharge from a chronic ulcer on the plantar aspect of his left foot.
- Treated twice with oral antibiotics in the past, without improvement. Recently developed low-grade fevers and difficulty walking.
- Past medical history: Type 2 diabetes, hypertension, peripheral neuropathy.
- MRI consistent with osteomyelitis involving 1st metatarsal, with adjacent soft tissue gas and abscess formation.
- Wound culture: mixed flora, including anaerobes *(Bacteroides fragilis, Peptostreptococcus)*.
- Plan: surgical debridement, ceftriaxone + metronidazole x6 weeks.

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Question #4

What adverse effect of metronidazole is of most concern in this patient?

A. Nausea
B. Leukopenia
C. Disulfiram reaction
D. Metallic taste
E. Peripheral neuropathy

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Metronidazole-induced Peripheral Neuropathy

- Burning, tingling, numbness in feet/hands (stocking-glove pattern)
- Risk factors
  - Prolonged therapy (> 2-4 weeks)
  - High total dose
  - Pre-existing neuropathy (e.g., diabetes)
  - Other neurotoxic drugs (e.g., vincristine)
- Clinical features
  - Symmetric distal sensory neuropathy
  - ± Mild weakness, gait imbalance
  - Rare: central toxicity (ataxia, encephalopathy)
- Rule out: B12 deficiency, diabetes, alcoholism, other neurotoxins
- Management
  - Stop drug
  - Neuropathic pain meds, PT/OT for gait
- Prognosis
  - Expect recovery in weeks to month
  - Often reversible if recognized early
  - Incomplete recovery if exposure prolonged
- Antimicrobial stewardship
  - Counsel patient on early symptoms if long drug course planned
  - Periodically reassess need for metronidazole

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Case #5

- 65-yo man (5'11", weight 72 kg) is being treated for a forearm infection that has developed purulent drainage over the past few days.
- PMH includes hypertension and a MRSA infection last year.
- Current: T 38.0°C, other VS WNL. WBC 14.8, SCr 1.3 mg/dL (estimated CrCl 60 mL/min).
- Current meds: valsartan, chlorthalidone.
- Decision to incise and drain the wound, then begin TMP-SMX 2 DS tablets q12h until patient is afebrile x3-5 days.
- On the third day, the WBC is WNL, all VS are WNL (he is afebrile), but his SCr has increased to 1.6 mg/dL.

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Question #5

What would be the most reasonable course of action?

A. Continue TMP-SMX at the same dose
B. Continue TMP-SMX at a reduced dose
C. Discontinue TMP-SMX
D. Change to vancomycin IV (15-20 mg/kg IV q12h)
E. Change to dicloxacillin (500 mg PO q6h)

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TMP-SMX-Induced ↑SCr (without affecting glomerular filtration)

- Mechanism: TMP competes with creatinine for tubular secretion.
- Other drugs that can do this: bictegravir, cobicistat.
- Typical increase: around 20% (dose-dependent). So no, we don't expect it to get progressively worse.
- Can be confusing, since TMP-SMX is also actually associated with renal impairment via one of these mechanisms:
  - Acute interstitial nephritis
  - Crystalluria
  - Acute tubular necrosis (rare)
- Another pearl worth remembering: TMP-SMX can result in hyperkalemia
  - TMP acts like amiloride, a K+ sparing diuretic
  - More common at higher doses

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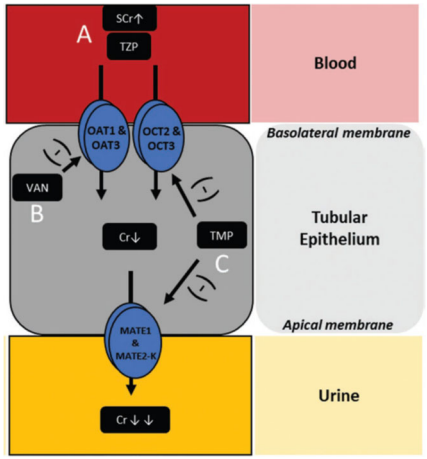

How TMP increases SCr without affecting without affecting glomerular filtration

GLOSSARY
TMP=trimethoprim
Cr=creatinine
OAT=organic anion transporter
OCT=organic cation transporter
MATE=multidrug and toxin extrusion

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Case #6

- 71-yo man presents to the ED complaining of jaundice for two weeks associated with itching and a mild rash involving his limbs and torso. He also mentions his urine is dark brown.
- No fever, headache, myalgias, arthralgias, respiratory symptoms, abdominal pain, nausea, vomiting, diarrhea, anorexia, or weight loss.
- NKA, no recent or distant exposure to alcohol or illicit drugs, non-smoker.
- Abdominal imaging: no relevant findings.
- Lab: hyperbilirubinemia, increased alkaline phosphatase. Mild AST/ALT elevations.
- Two days ago, finished a 14-day course of an antibiotic for a respiratory infection.

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Question #6

Which of the following oral antibiotics (he might have taken) is most associated with drug-induced liver disease?

A. Moxifloxacin
B. Azithromycin
C. Cefuroxime axetil
D. Doxycycline
E. Amoxicillin-clavulanate

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Amoxicillin-Clavulanate Induced Liver Disease

- One of the most common causes of drug-induced liver disease (DILI).
- More common than with amoxicillin alone.
- Risk factors: male sex, age >55, alcohol consumption, repeated use of the drug, use of other hepatotoxic drugs.
- Average onset: 3 weeks after initiation of therapy.
- Typical features: fatigue, fever, nausea, abdominal pain, pruritus, jaundice.
- Most common pattern of liver enzyme elevations: cholestatic. A mixed or hepatocellular pattern may be seen in younger patients.
- Usually reversible.

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Case #7

- 65-yo mildly obese man, renal transplant recipient. Immunosuppression regimen includes prednisone. Active lifestyle.
- Estimated CrCl: 45 mL/min.
- Prescribed levofloxacin 750 mg po q24h x14 days for prostatitis.
- After ten days, he complains of bilateral Achilles tendon (AT) pain. He says it began after 3-4 days of levofloxacin. He is switched to TMP-SMX to finish up his therapy.
- AT still painful 4 days later. Prednisone dose increased, apparently to maybe help with the pain.
- One month later, he loses his footing and slips, rupturing his left Achilles tendon.

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Question #7

Which fluoroquinolone is most associated with Achilles tendon rupture?

A. Gemifloxacin
B. Ciprofloxacin
C. Levofloxacin
D. Moxifloxacin
E. Delafloxacin

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Fluoroquinolone and tendons

- Inflammation or rupture of tendons, particularly the Achilles tendon (often bilateral).
- Tendinopathy: incidence 0.14% to 0.4%. Tendon rupture is rare (1-2 per 10,000 patients). Rupture is often preceded by tendinitis, but not always.
- Onset: within days to weeks, may be delayed for a few months.
- Symptoms: tenderness, swelling, stiffness, often accompanied by sharp pain with walking. Symptoms tend to occur acutely.
- Mechanism: unclear.
- Risk factors: See next slide. Statins do not seem to increase the risk.

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FQs, tendons, and the QTc interval: RISK FACTORS

FQ tendon rupture	QTc prolongation
Age >60	Older age
Concomitant steroid use	Female gender
Male gender	↑ baseline QT interval
Obesity	Bradycardia
↑cumulative days of FQ exposure	CHF
	Hypokalemia
	Hypomagnesemia
	Other QT-prolonging drugs

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Management of FQ Tendon Injury

- According to the FDA: At the first sign of tendon pain, swelling, or inflammation, patients should stop taking the FQ, avoid exercise and use of the affected area, and promptly contact their health care provider for evaluation and transition to a non-FQ alternative.
- Nonsurgical management strategies for tendinopathy include analgesics, PT, and/or immobilization.
- Surgical intervention may be required in severe cases.
- Most patients recover within a month without debilitating consequences, but in some cases, recovery takes 6 months or longer. Swelling, pain, or difficulty walking may occasionally become long-term complications.

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Case #8

- A 68-yo man (5'10", weight 110 kg) complains of fatigue, easy bruising, and gum bleeding.
- Past medical history includes obesity, type 2 diabetes, hypertension, CKD, and chronic osteomyelitis of his right foot.
- Underwent surgical debridement of his right foot 3 weeks ago.
- SCr 1.6 mg/dL (estimated CrCl 55 mL/min)
- Current meds: linezolid 600 mg po q12h (started at the time of surgery), metformin, lisinopril, and aspirin.
- VS within normal limits. Hemoglobin 9.1 g/dL, hematocrit 27%, WBC 2,100/µL, platelets 62,000 /µL, reticulocytes low. B12, folate normal.

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Question #8

Which of the following is the most important risk factor for linezolid myelosuppression in this patient?

A. Renal impairment
B. Treatment duration >2 weeks
C. Obesity
D. Treatment with lisinopril
E. Diabetes

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Linezolid-induced Myelosuppression

- A reversible pancytopenia
  - Lack of blasts/dysplasia on smear or marrow biopsy
- Risk factors
  - Treatment >14 days (probably most important)
  - Older age
  - Renal dysfunction
  - Concomitant marrow-toxic drugs
- Monitoring recommendation
  - Weekly CBC w/diff for treatment >14 days
- Management
  - Stop drug, switch to alternate agent if necessary
  - Monitor blood counts closely
  - Heme consult if counts continue to decline or fail to recover
  - Recovery expected within 1-2 weeks

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Case #9

- A 63-yo man (73 kg, 5'11") is admitted with worsening back pain.
- Past medical history: type 2 diabetes.
- Allergy: Ceftriaxone (urticaria).
- Blood cultures on admission: *E. faecalis*, pan-sensitive.
- Renal SCr: 1.3 mg/dL (estimated CrCl 62 mL/min).
- TEE: mitral valve vegetation. MRI: L5/S1 vertebral osteomyelitis.
- Treatment proposed: ampicillin 2 gm IV q4h + gentamicin 70 mg IV q8h (both x6-8 weeks).

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Question #9

Which of the following is the most important management concern specific to this patient?

A. Inability to give ampicillin + gentamicin to an outpatient
B. Drug-induced nephrotoxicity
C. Target gentamicin levels are not well-defined in this setting
D. Drug-induced ototoxicity
E. Use of ampicillin in someone with ceftriaxone allergy

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NEPHROTOXICITY	OTOTOXICITY
Reversible	Irreversible
Well defined risk factors*	Poorly defined risk factors
Well defined time course	Poorly defined time course
Monitor SCr	No easy labs to follow
Serum drug concentrations correlate well	Serum drug concentrations correlate poorly

*advanced age, duration of therapy, hypotension, concomitant liver disease, use of other nephrotoxins

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Case #10

- 53-yo man in the ED secondary to a witnessed seizure and loss of consciousness.
- Past medical history: alcohol abuse, seizure disorder.
- Seizures managed, patient treated empirically for meningitis (ceftriaxone 2 gm q12h, ampicillin 2 gm q4h, vancomycin 1 gm q12h, dexamethasone).
- Head CT, LP findings unremarkable. Blood and urine cultures negative. CxR: RLL opacity. On day 2, ceftriaxone continued (same dose), other drugs discontinued. Azithromycin initiated (500 mg IV q24h).
- Day 7: patient jaundiced. Total bilirubin 5.8 mg/dL (↑), direct bilirubin 3.4 mg/dL (↑). Mild RUQ pain.
- RUQ ultrasound: biliary sludge and cholelithiasis, no evidence of cholecystitis.

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Question #10

Which drug is the likely explanation for these observations?

A. Azithromycin
B. Ceftriaxone
C. Vancomycin
D. Ampicillin
E. Dexamethasone

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Ceftriaxone Pseudocholelithiasis

- Drug excreted in bile in high concentrations.
- Can form gallstones consisting of a ceftriaxone-calcium complex (often referred to as biliary sludge). Typically happens around day 9 of treatment.
- Risk factors include:
  - High doses
  - Prolonged therapy
  - Dehydration
  - Receipt of parenteral nutrition
  - Hypercalcemia
- May be more common in children. There are may also be genetic factors.
- Presentation: RUQ tenderness, nausea.
- LFTs: Usually a cholestatic pattern.
- Drug discontinuation usually solves the problem.
- Resolution of sludge can take about 2 weeks.

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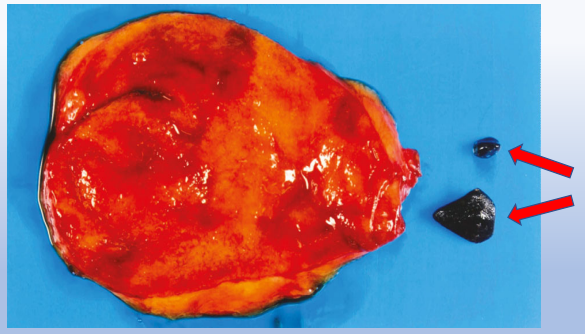

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