Antimicrobial Therapy II: More Toxicities and Pharmacologic Issues You Should Know

Douglas Black, PharmD
University of Washington

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor, *The Sanford Guide to Antimicrobial Therapy*

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Case vignette #1

- A 22-yo woman presents with acute onset chest pain and painful swallowing that started 2 days ago.
- 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 acne vulgaris five days ago.
- Suspicion: drug-induced (pill) esophagitis.

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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.
- Characterized by sudden onset odynophagia, retrosternal chest pain, dysphagia.
- Symptoms appear hours (even days) after drug ingestion.
- Risk factors:
  - Supine position after drug ingestion, inadequate water intake
  - Pre-existing esophageal motility disorder
  - Older age
  - Large or multiple medications
- Management:
  - Discontinue offending agent, hydration, soft diet
  - Supportive treatments: sucralfate, PPIs, viscous lidocaine

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Other antimicrobials associated with pill esophagitis

- Azithromycin
- Clindamycin
- Penicillins (rare)
- Rifampin
- Tetracyclines (most common)
- TMP-SMX

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Case vignette #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 WNL
- Four days ago, began valacyclovir 1 gm q8h for shingles.

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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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(Val)acyclovir neurologic toxicity

- Presentation
  - Early: agitation, hallucinations, confusion, disorientation
  - Later: tremor, myoclonus, delirium
  - Rare: seizures, extrapyramidal symptoms
- Risk factors: renal impairment, age, high doses, dehydration
- Pathophysiology: accumulation of CMMG (9-carboxymethoxymethylguanine)
- Management
  - Stop drug
  - Adjust dosage if therapy must continue
  - Hydration
  - Hemodialysis (extreme cases)

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Other antimicrobials associated with neurotoxicity

- Beta-lactams (seizures, encephalopathy)
- Ethambutol (optic neuritis, peripheral neuropathy)
- Fluoroquinolones (confusion, seizures, peripheral neuropathy, exacerbation of myasthenia gravis)
- Isoniazid (peripheral neuropathy, encephalopathy, psychosis, seizures)
- Linezolid (peripheral neuropathy, optic neuropathy, serotonin syndrome)
- Metronidazole (peripheral/optic/autonomic neuropathy, encephalopathy)
- Nitrofurantoin (peripheral neuropathy)

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Case vignette #3

- A 52-yo man presents to the ED with an itchy rash, angioedema, and fever (T 39.2°C) that started 24 hours ago. The rash began as diffuse erythematous papules on his neck that spread down his torso to his arms and legs.
- 4 weeks ago, a planned 6-week course of vancomycin was begun after surgical debridement for right fifth digit osteomyelitis.
- The next day, the rash has spread to his palms and soles, and there is concern for impending airway compromise due to facial swelling. He is admitted to the ICU.
- Significant lab findings: eosinophils 2025 cells/μL, elevated IgE, atypical lymphocytes, evidence of AKI. AST/ALT WNL.
- Blood cultures, ANA, HIV, and HSV serologies negative. Skin biopsy shows spongiotic dermatitis with perivascular eosinophils.

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What is the antimicrobial agent most commonly associated with DRESS in the US?

a. TMP-SMX

b. Minocycline

c. Fluconazole

d. Azithromycin

e. Vancomycin

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- T-cell-mediated SCAR most commonly associated with ASMs, antibiotics, allopurinol, and NSAIDs.
- Delayed type IV hypersensitivity reaction.
- Typical latency: 2-6 weeks.
- Clinical presentation:
  - Rash, fever
  - Facial edema
  - Lymphadenopathy
  - Eosinophils >700 cells/μL, atypical lymphocytosis
  - Internal organ involvement
- RegiSCAR can be helpful
- Management:
  - Stop drug, supportive care
  - Corticosteroids

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Antimicrobials associated with DRESS

- Vancomycin
- TMP-SMX
- β-lactams: amoxicillin, ceftriaxone, piperacillin-tazobactam
- Tetracyclines: doxycycline, minocycline
- Clindamycin
- Nitrofurantoin
- Antitubercular drugs: INH, rifampin, PZA, ethambutol
- Antivirals: nevirapine
- Dapsone

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Case vignette #4

- A 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.
- PMH: 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
- Plan: surgical debridement, ceftriaxone 2 gm IV q24h + metronidazole 500 mg q8h x6 weeks.

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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 neurotoxins (e.g., vincristine).
- Clinical features:
  - Symmetric distal sensory neuropathy
  - ± Mild weakness, gait imbalance
  - Rare: central toxicity (ataxia, encephalopathy)
- Management: stop drug, neuropathic pain meds, PT/OT for gait.
- As with other drugs, recovery is slow (weeks to months). Often reversible if recognized early. Prolonged exposure may mean incomplete recovery.

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Case vignette #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: hypertension, 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).
- Meds: valsartan, chlorthalidone.
- Decision to incise and drain the wound, then begin TMP-SMX 2 DS tablets q12h until he is afebrile x3-5 days.
- On the third day, the WBC and all VS are WNL (he is afebrile), but his SCr has increased to 1.6 mg/dL.

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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 q12h)

e. Change to dicloxacillin (500 mg po q6h)

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

- Trimethoprim can compete with creatinine for tubular secretion.
- Typical increase in SCr: around 20% (dose-dependent). Not expected 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)
- Also 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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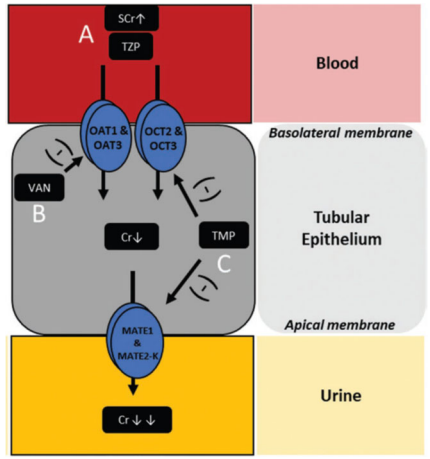

How TMP increases SCr without affecting without affecting glomerular filtration

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Case vignette #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 mentions his urine is dark brown.
- No fever, headache, myalgias, arthralgias, respiratory symptoms, abdominal pain, nausea, vomiting, diarrhea, anorexia, or weight loss.
- NKA, no 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, he finished a 14-day course of an antibiotic for a respiratory infection.

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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 amoxicillin alone.
- Risk factors: male sex, age >55, ethanol consumption, repeated use of the drug, other hepatotoxic drugs. Duration of treatment might be another risk factor.
- Average onset: 3 weeks after start 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 (might take 6 months).

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Other antimicrobials associated with drug-induced liver disease

- Antimycobacterials: INH, PZA, rifampin, bedaquiline
- Macrolides (especially erythromycin)
- Minocycline (autoimmune hepatitis)
- Oxacillin
- Terbinafine
- TMP-SMX
- Azole antifungals
- Nevirapine

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Case vignette #7

- 65-yo mildly obese man, renal transplant recipient. Anti-rejection regimen includes prednisone. Active lifestyle.
- Estimated CrCl is 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 3-4 days after starting levofloxacin. He is switched to TMP-SMX to finish up his therapy.
- AT still painful 4 days later. Prednisone dose increased.
- One month later, he loses his footing and slips, rupturing his left AT.

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Which fluoroquinolone is most associated with Achilles tendon rupture?

a. Gemifloxacin

b. Ciprofloxacin

c. Levofloxacin

d. Moxifloxacin

e. Delafloxacin

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Fluoroquinolones and tendon toxicity

- FQs can cause 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 (there are theories).
- 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

- 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 seek evaluation and possible transition to a non-FQ alternative drug.
- 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 vignette #8

- A 68-yo man (5'10", weight 110 kg) complains of fatigue, easy bruising, and gum bleeding.
- PMH: obesity, type 2 diabetes, hypertension, CKD, 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 3 weeks ago), metformin, lisinopril, and aspirin.
- VS WNL. Hemoglobin 9.1 g/dL, hematocrit 27%, WBC 2,100/µL, platelets 62,000/µL, reticulocytes low. B12, folate WNL.

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What 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
  - Older age
  - Renal dysfunction
  - Concomitant marrow-toxic drugs
- Monitoring recommendation
  - Weekly CBC w/diff if treatment >14 days.
- Management
  - Stop drug, switch to alternative agent.
  - Monitor CBC. Heme consult if counts continue to decline or fail to recover.
  - Recovery expected within 1-2 weeks.

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Other antimicrobials associated with myelosuppression

- Beta-lactams (e.g., nafcillin, piperacillin-tazobactam)
- Chloramphenicol
- Flucytosine
- Ganciclovir, valganciclovir
- Pyrimethamine
- TMP-SMX
- Zidovudine

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Case vignette #9

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

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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 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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Other antimicrobials associated with ototoxicity

- Aminoglycosides
- Capreomycin
- Macrolides (especially erythromycin)
- Vancomycin

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Case vignette #10

- 53-yo man in the ED s/p seizure, loss of consciousness.
- PMH: alcohol abuse, seizure disorder. Renal function WNL.
- Seizures managed, empiric tx for meningitis (ceftriaxone 2 gm q12h, ampicillin 2 gm q4h, vancomycin 1 gm q12h, dex).
- Head CT, LP findings unremarkable. Blood, urine cultures negative. CxR: RLL opacity. Day 2: ceftriaxone continued, other drugs discontinued, azithromycin added (500 mg IV q24h).
- Day 7: patient jaundiced. T bili 5.8 mg/dL (↑ from 2.1), D bili 3.4 mg/dL (↑ from 0.7). Mild RUQ pain.
- RUQ ultrasound: biliary sludge and cholelithiasis, no evidence of cholecystitis.

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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

- Ceftriaxone is excreted in the bile in high concentrations (1000s of µg/mL).
- Gallstones consisting of a ceftriaxone-calcium complex (often referred to as biliary sludge) can form, typically around day 9 of treatment.
- Risk factors: high doses, prolonged therapy, dehydration, parenteral nutrition, hypercalcemia.
- May be more common in children. There may also be genetic factors.
- Presentation: RUQ tenderness, nausea.
- LFTs: typically a cholestatic pattern.
- Stopping the drug is usually enough.
- Resolution of sludge takes ≈2 weeks.

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Case vignette #11

- A 58-year-old man presents to the ED 45 minutes after experiencing sudden-onset nausea, flushing, palpitations, and vomiting.
- These symptoms began 20 minutes after consuming 2 glasses of red wine.
- Two days ago, he was started on metronidazole 500 mg po q8h for suspected *C. difficile* colitis.
- No known drug allergies. He takes no other medications.

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Which of the following best explains this reaction?

a. Metronidazole-induced serotonin syndrome

b. Type 1 hypersensitivity reaction to metronidazole

c. Acetaldehyde accumulation

d. Ethanol-induced inhibition of metronidazole metabolism

e. The mechanism of this reaction is disputed

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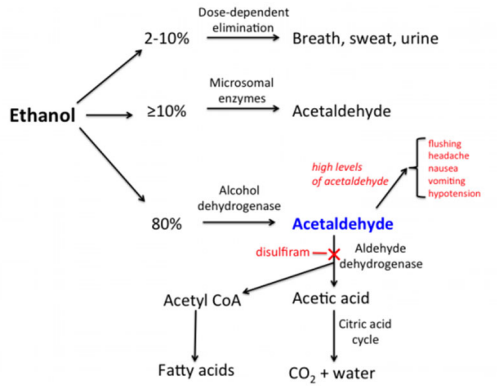
Ethanol Metabolism



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