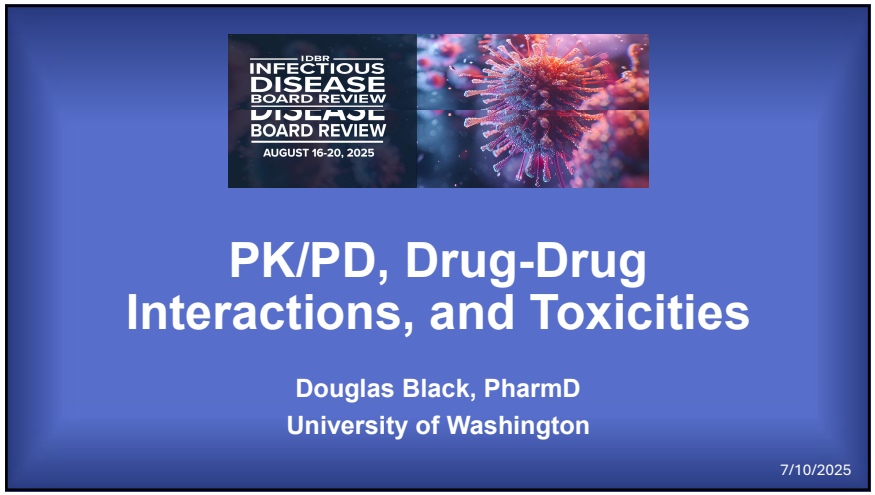
7 Principles of Antimicrobial Therapy for Exam: What You Need to Know About Toxicities, PK/PD, Drug-Drug Interactions

Douglas Black, PharmD



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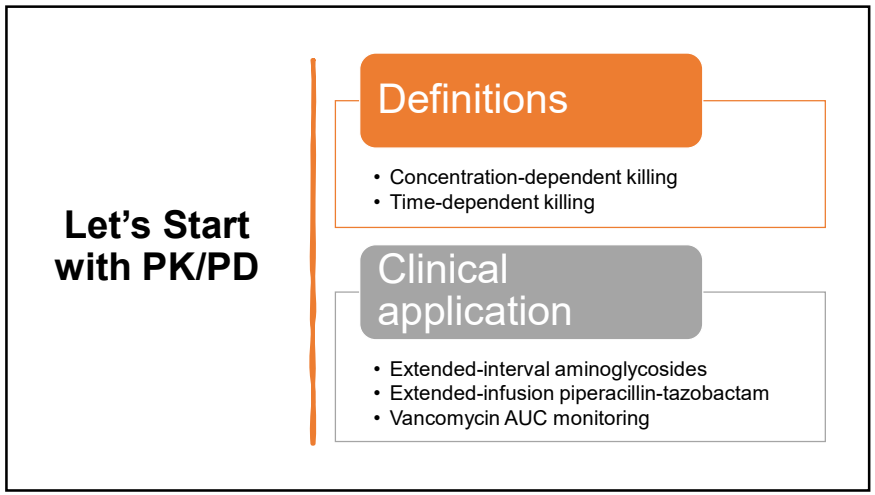

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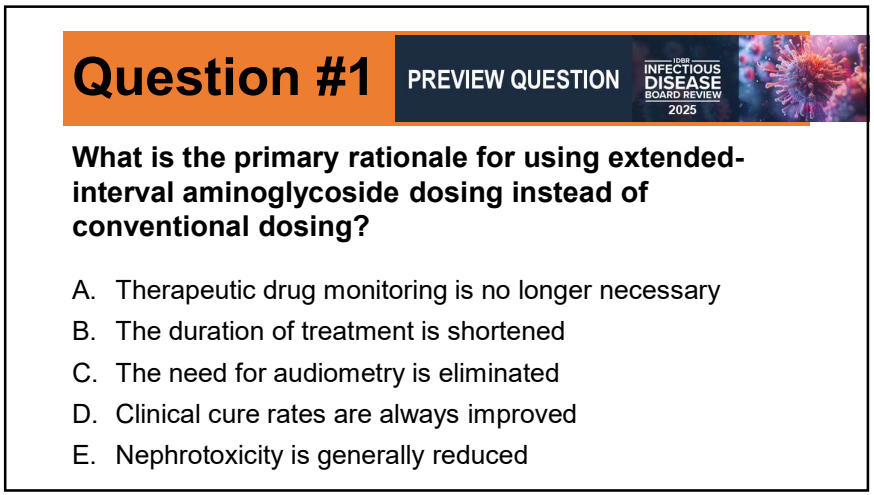

4

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Question #1

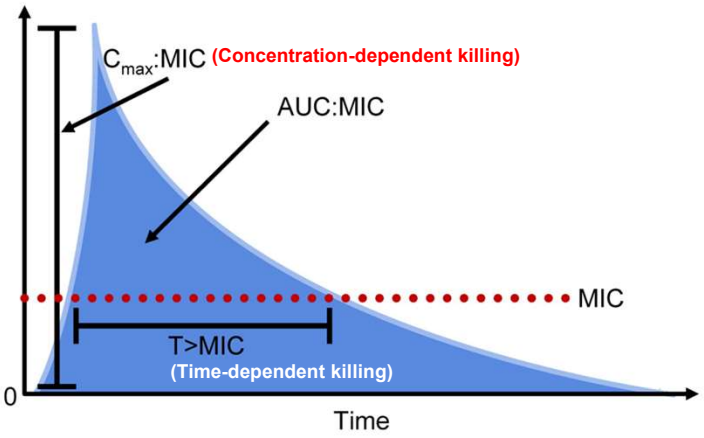
PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

What is the primary rationale for using extended-interval aminoglycoside dosing instead of conventional dosing?

A. Therapeutic drug monitoring is no longer necessary
B. The duration of treatment is shortened
C. The need for audiometry is eliminated
D. Clinical cure rates are always improved
E. Nephrotoxicity is generally reduced *

5



6

Conventional or Extended-Interval Aminoglycoside Dosing?

	Aerobic gram-positive infection	Aerobic gram-negative infection
Conventional dosing	**Preferred**	Use certain situations*
Extended-interval dosing	OK for certain types of streptococcal endocarditis	**Preferred**

*Burns >20% BSA, cystic fibrosis, age <12 years, ascites, obesity, poor renal function

7

The Simplicity of Extended-Interval Dosing for Gram-negative Infection

CrCl	Initial Dosage interval*
≥60	7 mg/kg q24h
40-59	7 mg/kg q36h
20-39	7 mg/kg q48h
<20	Use conventional dosing

*Based on ideal BW, or adjusted BW if obese

8

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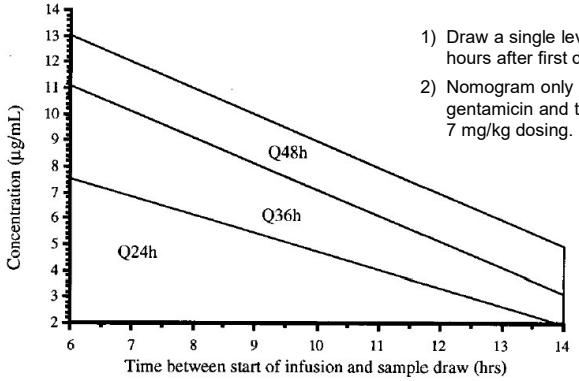
Using the Hartford Nomogram



1) Draw a single level 6-14 hours after first dose.
2) Nomogram only applies to gentamicin and tobramycin, 7 mg/kg dosing.

Antimicrob Agents Chemother 1995;39:650-55

9

Summary: Antibacterial Pharmacodynamics

Activity	Killing	PAE	PD index	Drugs
Bactericidal	Time-dependent	Minimal*	T>MIC	β-lactams
Bactericidal	Concentration-dependent	Prolonged	Cmax:MIC AUC:MIC	Aminoglycosides Colistin Daptomycin Fluoroquinolones Metronidazole
Bacteriostatic	Concentration-dependent	Moderate to prolonged	AUC:MIC	Clindamycin Linezolid Macrolides Tetracyclines Tigecycline Vancomycin

*Exception: carbapenems (prolonged post antibiotic effect vs. gram-negative bacilli)

10

Question #2

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

What is one documented benefit of extended-infusion piperacillin-tazobactam?

A. Less *C. difficile* infection is observed
B. Clinical outcomes are improved in some patients
C. The emergence of resistant isolates is reduced
D. The need for renal dosage adjustment is eliminated
E. CNS penetration of piperacillin is improved

11

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12

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Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

Thomas P. Lodise, Jr.,[1,2] Ben Lomaestro,[3] and George L. Drusano[2]

[1]Department of Pharmacy Practice, Albany College of Pharmacy, [2]Ordway Research Institute, and [3]Department of Pharmacy, Albany Medical Center Hospital, Albany, New York

Background. Piperacillin-tazobactam is frequently used to treat *Pseudomonas aeruginosa* infections in critically ill patients. In an effort to improve clinical outcomes, an extended-infusion dosing scheme for piperacillin-tazobactam therapy was devised using a Monte Carlo simulation and was adopted into clinical practice at Albany Medical Center (Albany, New York). This study evaluates the clinical implications of extended infusion of piperacillin-tazobactam therapy for critically ill patients with *P. aeruginosa* infection.

Methods. We performed a cohort study of patients who received piperacillin-tazobactam therapy for a *P. aeruginosa* infection that was susceptible to piperacillin-tazobactam during the period January 2000–June 2004. Prior to February 2002, all patients received intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 h); after this time, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 h every 8 h). Data on demographic characteristics, disease severity, and microbiology were collected, and outcomes were compared between groups.

Results. A total of 194 patients comprised the 2 study groups: 102 patients received extended infusions of piperacillin-tazobactam, and 92 patients received intermittent infusions of piperacillin-tazobactam. No differences in baseline clinical characteristics were noted between the 2 groups. Among patients with Acute Physiological and Chronic Health Evaluation–II scores ≥17, 14-day mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; $P = .04$), and median duration of hospital stay after collection of samples for culture was significantly shorter for patients who received extended-infusion therapy than for patients who received intermittent-infusion therapy (21 days vs. 38 days; $P = .02$).

Conclusions. These results indicate that extended-infusion piperacillin-tazobactam therapy is a suitable alternative to intermittent-infusion piperacillin-tazobactam therapy, and they strongly suggest that improved outcomes may be realized by administering extended-infusion piperacillin-tazobactam therapy to critically ill patients with *P. aeruginosa* infection.

EI: 3.375 gm (over 4h) q8h
II: 3.375 gm (over 30 min) q4-6h

APACHE II ≥17
EI: n=41
II: n=38

Clin Infect Dis 2007;44:357-63

13

Question #3

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

What is the correct vancomycin AUC to target for treating MRSA pneumonia?

A. 100-200 µg*hr/mL
B. 200-400 µg*hr/mL
C. 200-600 µg*hr/mL
D. 400-600 µg*hr/mL
E. 400-800 µg*hr/mL

14

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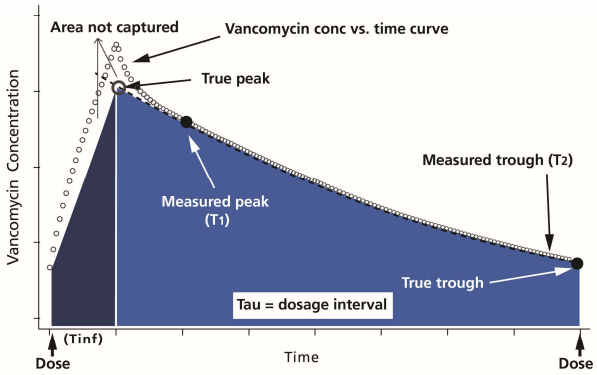

16

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Vancomycin AUC Monitoring Pearls

- For serious MRSA infections, an AUC of 400-600 should be targeted. MIC is assumed to be 1. This approach will minimize the risk of AKI and maximize efficacy, compared to trough-only monitoring.
- For other pathogens or infections, the routine use of AUC monitoring is not well established and requires further study.
- There are pros and cons to the two methods of determining AUC (trapezoidal equations vs. Bayesian methods).
- If administering vancomycin by continuous infusion, simply multiple steady-state concentration by 24 to calculate AUC_{24}.

17

Drug-Drug Interactions

Pharmacodynamic

Pharmacokinetic

- CYP450-mediated
- Transporter-mediated

18

Question #4

- A 72-year-old woman presents to the ED complaining of lightheadedness and a fainting spell
- Increasing fatigue and palpitations over the last 3 days
- Recently diagnosed with an LRI, prescribed clarithromycin 500 mg po bid 4 days ago
- Other problems: atrial fibrillation, hypertension, hyperlipidemia, type 2 diabetes
- Meds: candesartan, amiodarone, metoprolol, atorvastatin, metformin

19

Question #4

A drug-drug interaction between clarithromycin and which drug below best explains this patient's syncopal episode?

A. Candesartan
B. Amiodarone
C. Metoprolol
D. Atorvastatin
E. Metformin

20

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B. **Amiodarone ***
C. Metoprolol
D. Atorvastatin
E. Metformin

21

Question #5

- A 67-year-old woman presents to her primary care provider with persistent dysuria and urinary frequency x5 days
- Started ciprofloxacin 500 mg po bid by urgent care 3 days ago for presumed UTI
- Denies flank pain, fever, hematuria
- PMH: GERD, hypertension, osteoarthritis
- Meds: lisinopril, losartan, omeprazole, sucralfate, acetaminophen

22

Question #5

Administration of which medication should be staggered, if possible, to avoid interacting with ciprofloxacin?

A. Lisinopril
B. Losartan
C. Omeprazole
D. Sucralfate
E. Acetaminophen

23

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Administration of which medication should be staggered, if possible, to avoid interacting with ciprofloxacin?

A. Lisinopril
B. Losartan
C. Omeprazole
D. **Sucralfate ***
E. Acetaminophen

24

Question #6

- A 75-year-old man started TMP-SMX one DS tablet q12h five days ago for acute prostatitis
- Allergy: levofloxacin (tendon pain)
- He now reports new-onset bruising, bleeding gums, and blood in his stool this morning
- No recent trauma or prior bleeding issues
- Other problems: atrial fibrillation, hypertension, type 2 diabetes
- Meds: warfarin, metformin, amlodipine

25

Question #6

What is the most likely explanation for these bleeding symptoms?

A. Inhibition of warfarin metabolism
B. Protein binding displacement
C. Alteration of vitamin-K producing gut flora
D. Myelosuppression from TMP-SMX
E. Changes in the patient's diet

26

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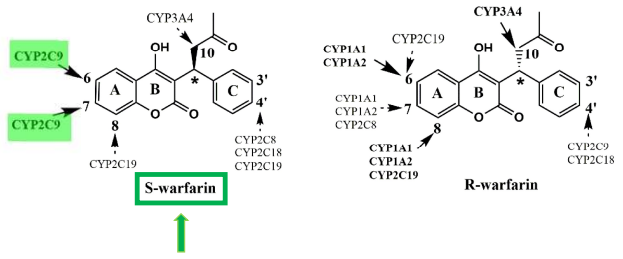
27

Warfarin Enantiomers and CYP450



3-5x as active as the R-enantiomer

28

Question #7

- A 38-year-old woman has focal epilepsy that is well controlled on phenytoin x3 years
- She presents with new-onset breakthrough seizures
- Two weeks ago, she began treatment for LTBI (rifampin 600 mg daily)
- Serum phenytoin level is 3.2 µg/mL (reference range: 10–20 µg/mL)

29

Question #7

Which of the following best explains the cause of her breakthrough seizures?

A. Rifampin reduces gastrointestinal absorption of phenytoin
B. Rifampin induces hepatic enzymes, lowering phenytoin serum levels
C. Rifampin displaced phenytoin from plasma proteins, increasing clearance
D. Rifampin inhibits P-glycoprotein, reducing phenytoin CNS penetration
E. Rifampin binds directly to phenytoin, inactivating it in the plasma

30

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E. Rifampin binds directly to phenytoin, inactivating it in the plasma

31

Question #8

- 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

32

Question #8

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

33

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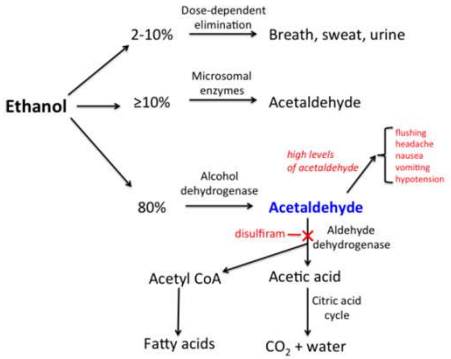
34

Ethanol Metabolism



35

Question #9

- A 42-year-old woman presents with acute agitation, diaphoresis, muscle stiffness, and tremors
- 24 hours ago, she began linezolid 600 mg po q12h for a community-acquired MRSA skin infection
- History of major depressive disorder, takes sertraline 100 mg po q24h
- Other problems: migraine (prn treatment with sumatriptan)
- VS: T 39.2°C, HR 124, BP 159/86, RR 22

36

Question #9

What is the most appropriate initial management?

A. Discontinue linezolid and sertraline, give IV fluids and benzodiazepines
B. Switch from sertraline to fluoxetine
C. Start cyproheptadine, continue linezolid with dose adjustment
D. Observe without intervention unless seizures occur
E. Continue linezolid and sertraline, add propranolol for symptom control

37

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D. Observe without intervention unless seizures occur
E. Continue linezolid and sertraline, add propranolol for symptom control

38

Question #10

- A 67-year-old man presents with a 3-day history of increasing muscle pain and weakness in his thighs and calves, and dark colored urine this morning
- Problems: hyperlipidemia, hypertension, onychomycosis (recently diagnosed)
- Meds: simvastatin 40 mg qd (x4 years), metformin 1 gm bid, lisinopril 10 mg qd, itraconazole 200 mg qd (started 6 days ago)
- Labs: CK 12,400 U/L, SCr 1.4 mg/dL (baseline 1.0), mild AST/ALT elevation. UA: myoglobinuria

39

Question #10

Which of the following is a recognized risk factor for statin myopathy in the setting of oral antifungal therapy?

A. Use of a statin metabolized by CYP1A2
B. Rosuvastatin use
C. Co-administration with metformin
D. Young age
E. Concomitant use of a moderate to strong CYP3A4 inhibitor

40

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C. Co-administration with metformin
D. Young age
E. Concomitant use of a moderate to strong CYP3A4 inhibitor *

41

Question #11

- A 72-year-old female complains of progressive weakness, lightheadedness, and occasional palpitations x3 days
- No chest pain or SOB
- Yesterday completed a five-day course of TMP-SMX (1 DS tab bid) for a UTI
- PMH: hypertension, CKD (CrCl ≈ 50), type 2 diabetes.
- Meds: losartan 100 mg qd, amlodipine 5 mg qd, metformin 500 mg bid
- Labs: K^+ 6.4 mEq/L, SCr 1.5 mg/dL
- ECG: peaked T waves, bradycardia

42

Question #11

Which of the following prescribing practices would have been the best way to avoid this situation?

A. Use nitrofurantoin instead of TMP-SMX
B. Hold the metformin during the course of TMP-SMX
C. Prescribe TMP-SMX at a reduced dose
D. Replaced losartan with lisinopril
E. Discontinue the amlodipine

43

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D. Replaced losartan with lisinopril
E. Discontinue the amlodipine

44

Question #12

- A 27-yo woman presents with a severely infected dog bite on her right hand
- You plan to prescribe a course of amoxicillin-clavulanate
- She is taking an oral contraceptive that contains 35 µg of ethinyl estradiol and 0.25 mg of norgestimate
- She asks if she should use condoms while taking the antibiotic

45

Question #12

Which of the following antimicrobial agents is most clearly associated with reducing the efficacy of oral contraceptives?

A. Amoxicillin-clavulanate
B. Doxycycline
C. Rifampin
D. Azithromycin
E. Ciprofloxacin

46

Question #12

Which of the following antimicrobial agents is most clearly associated with reducing the efficacy of oral contraceptives?

A. Amoxicillin-clavulanate
B. Doxycycline
C. Rifampin *
D. Azithromycin
E. Ciprofloxacin

47

Drug-Drug Interaction Resources

HIV, Hepatitis and COVID drug interaction information from The University of Liverpool and The University of Basel

HIV Drug Interactions
www.hiv-druginteractions.org

HEP Drug Interactions
www.hep-druginteractions.org

Covid19 Drug Interactions
www.covid19-druginteractions.org

48

Antimicrobial Toxicities

49

Case #13

- A 72-year-old man with a history of CKD and hypertension is admitted with sepsis secondary to a UTI
- Cefepime 2 gm IV q12h + vancomycin 1 gm IV q12h are begun
- After 5 days of treatment, he begins to exhibit confusion, agitation, and tremors. His family reports that he has become increasingly disoriented and has had difficulty recognizing familiar faces
- His SCr, previously stable, is found to be elevated

50

Cefepime-induced Neurotoxicity

- Factors associated with CIN: age, renal function, total dose administered, cefepime trough concentration (>20 µg/mL).
- Mechanism: GABA inhibition.
- Median duration from drug initiation to onset of CIN: 4 days.
- Manifestations: altered mental status, myoclonus, non-convulsive status epilepticus.
- EEG may be helpful, although no specific findings.
- Prognosis favorable. Most cases improve within 3 days of drug discontinuation.

J Antimicrob Chemother 2022;77:2908-2921

51

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/optic neuropathy, serotonin syndrome)
- Metronidazole (peripheral/optic/autonomic neuropathy, encephalopathy)
- Nitrofurantoin (peripheral neuropathy)

52

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Case #14

- A 64-year-old woman presents to the ED with a painful left arm at a previous IV site.
- PMH: atrial fibrillation, type 2 diabetes
- She is diagnosed with superficial thrombophlebitis and sent home. She returns 7 days later with fever and hypotension. Piperacillin-tazobactam + vancomycin are begun
- BC: positive for MSSA. TTE: no vegetations. She is switched to nafcillin 2 gm IV q4h, planned duration 2 weeks
- On day 9, routine lab work shows SCr to be 2.1 mg/dL (baseline 0.8), with eosinophilia. A rash on her chest and back is also observed

53

Acute Interstitial Nephritis

- Usually due to drug-induced hypersensitivity. Some infections (HIV, hepatitis) and immune disorders (lupus) have also been implicated.
- Typically presents after 2-3 weeks of drug therapy.
- Non-oliguric renal dysfunction (↑BUN, Scr) often gets our attention first.
- The "classic" triad (fever, rash, eosinophilia) is seen in <33% of patients. Some say the triad includes arthralgia, not eosinophilia. Patients may complain of flank pain.
- Definitive diagnosis requires kidney biopsy (generally not done).
- Full recovery usually occurs after the offending drug is stopped. Oral steroids have no established role.
- The patient's allergy history should be correctly labeled. Probably drug (not class) specific.

54

Drugs Associated with Acute Interstitial Nephritis

- Beta-lactams (penicillins, cephalosporins)
- Rifampin
- TMP-SMX
- Allopurinol
- Immune checkpoint inhibitors
- NSAIDs
- Proton pump inhibitors

55

Case #15

- A 45-year-old man with a history of type 2 diabetes and recent diagnosis of MRSA bacteremia started daptomycin therapy 7 days ago
- He presents with acute onset of dyspnea, dry cough, and fever, which has worsened over the past 24 hours
- Exam: febrile, tachypneic, and has bilateral crackles on lung auscultation
- Chest X-ray shows bilateral infiltrates consistent with pneumonia
- Lab: elevated eosinophil count.

56

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Daptomycin-induced Eosinophilic Pneumonia

- Rare but potentially severe.
- Pathogenesis unestablished.
- Unclear if DIEP is dose-related.
- Onset typically 2-4 weeks.
- Clinical features: new-onset fever, progressive dyspnea, cough (usually non-productive), diffuse bilateral pulmonary infiltrates, hypoxemia.
- Also observed: peripheral eosinophilia, elevated inflammatory markers (ESR, CRP).
- BAL: >25% eosinophils, or eosinophilic pneumonia at lung biopsy.
- Clinical improvement after discontinuation of daptomycin, administration of corticosteroids.

Open Forum Infect Dis 2022;9:ofac577

57

Case #16

- A 44-yo woman with AML undergoes allogeneic HSCT
- Course is complicated by severe GVHD with liver and intestinal involvement, treated with high-dose corticosteroids and infliximab
- Develops disseminated *Scedosporium apiospermum* infection with multiorgan involvement
- Treated with IV voriconazole, then oral voriconazole adjusted to maintain a trough concentration of 1.5-5 µg/mL
- 9 months after starting therapy, she complains of severe, disabling bone pain, arthralgias, and swelling of her hands and fingers

58

Voriconazole-associated Periostitis

- Prevalence not known.
- Features: generalized bone pain, ↑alkaline phosphatase, evidence of periostitis and/or exostoses on x-ray.
- Any bones can be affected, but the most common are ribs, forearms, legs, and shoulders.
- Takes a long time to occur, at least six weeks but often much longer.
- Cause: excess fluoride exposure.
- Related to voriconazole dose.
- CYP2C19 ultrarapid metabolizers may have increased generation of free fluoride (as well the need for a high voriconazole dose).
- Resolves within 2 months of drug discontinuation.

59

Case #17

- A 78-year-old woman being treated for UTI presents with recent symptoms of dyspnea, fatigue, and productive cough
- VS normal, no rash
- PMH: history of recurrent *E. coli* UTI, including an episode 4 months ago (treated with nitrofurantoin)
- Non-smoker
- Started another course of nitrofurantoin 3 days ago (100 mg bid x5 days)
- Chest X-ray: bilateral interstitial infiltrates, patchy ground-glass opacities, pleural effusion
- Lab: WBC 13,500/µL, eosinophils 10%. Other labs WNL

60

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Nitrofurantoin Pulmonary Toxicity: Acute

- Occurs in about 1 in 5000 patients.
- Typically presents about 9 days after a short course of therapy in women, age 60-70. Onset is shorter in repeat exposures.
- Think of as a hypersensitivity reaction (type I or III).
- Common symptoms: fever, dyspnea, cough, rash.
- PE: inspiratory crackles.
- Lab: eosinophilia, leukocytosis, elevated ESR.
- Imaging: Diffuse parenchymal changes, pleural effusions.
- Treatment: stop drug, document as allergy, avoid re-exposure. Steroids of unproven benefit.
- Improvement within 24-48 hours, full recovery in a few weeks.

61

Nitrofurantoin Pulmonary Toxicity: Chronic

- Develops after several months or years of long-term therapy (women, age 60-70).
- A cell-mediated or toxic response, possibly to drug metabolites.
- Common symptoms: Dyspnea, dry cough, fatigue. Fever uncommon. Overall, symptoms less intense than in an acute reaction.
- PE: dry crackles.
- Lab: elevated serum gamma globulins, eosinophilia, elevated transaminases, elevated ESR. Maybe ANA+.
- Imaging: Parenchymal opacities. Ground glass opacities on CT. Pleural effusion uncommon.
- Higher risk of parenchymal injury.
- Treatment: stop drug. Steroids of unproven benefit. Clinical improvement in weeks to months, may not fully resolve.

62

Case #18

- A 68-yo female presents with complaints of dizziness and palpitations
- PMH: hypertension, type 2 diabetes
- One week ago, prescribed levofloxacin 500 mg po q24h for CAP
- VS stable, physical exam unremarkable
- ECG: QTc 520 ms. Baseline (6 months earlier) is 430 ms
- Lab: electrolytes WNL. Troponins negative, echo shows normal LV function

63

FQ-induced QTc Interval Prolongation

- Increases risk of serious ventricular arrhythmias (e.g., torsade de pointes).
- Mechanism: blockade of potassium channels.
- Risk factors
  - Older age
  - Female
  - Congenital long QT syndrome
  - Bradycardia
  - CHF
  - Hypokalemia, hypomagnesemia
  - Other QT-prolonging drugs
- Symptoms: palpitations, lightheadedness or dizziness, fatigue, syncope.
- Likelihood: moxifloxacin > levofloxacin > ciprofloxacin.
- Consider ECG monitoring in high-risk patients.

64

Antimicrobial Classes Associated with QTc-interval Prolongation

- Antiparasitics: antimony, antimalarials, fexinidazole
- ARVs: atazanavir, efavirenz, rilpivirine
- Azole antifungals
- Fluoroquinolones
- Macrolides
- Other antibacterials: gepotidacin, lefamulin
- Pentamidine
- Good Internet source: crediblemeds.org

65

66