UWTASP
tele-antimicrobial stewardship program

June 8th,2021

Agenda

- *Antibiotic side effects*
- Case Discussions
- Open Discussion

Antibiotics side effects are common

- Literature suggests up to 2.8% of hospitalization result from drug-interactions

Antibiotic related toxicities lead to many ED visits!

- The prevalence of emergency department visits for adverse drug events in the United States was estimated to be 4 per 1000 individuals in 2013 and 2014. The most common drug classes implicated were anticoagulants, **antibiotics**, diabetes agents, and opioid analgesics.

JAMA. 2016 Nov 22; 316(20): 2115–2125.

Case 1

- A 68 yo M with DM, HTN, and chronic atrial fibrillation presents to the ER with a GI bleed. Recently started an antibiotic for a mild SSTI
- His INR is 5.2. There have been no recent changes to his warfarin dose and review of his medical record shows that his INR is usually between 2-3.

Medications
- metformin
- metoprolol
- HCTZ
- simvastatin
- lisinopril
- warfarin
- and “an antibiotic”

Case 1 Audience Response

Which antibiotic was most likely prescribed?

A Bactrim

B Cephalexin

C Clindamycin

D Dicloxacillin

E Nafcillin

Discussion, Case 1

- Nearly ALL abx interact with warfarin due to elimination of bacteria that produce vitamin K but some antibiotics are more likely to cause problems.
- Inflammatory response may down-regulate metabolic enzymes
- **Mechanism: Sulfonamides impair hepatic metabolism (CYP 2C9) of oral anticoagulants**
- competition of protein binding may also play a role.
- Ciprofloxacin also an inhibitor of CYP2C9
- Management: Consider alternatives, otherwise, recommend close monitoring of INR

- Single-strength daily ppx is probably fine but still would recommend initial INR check.

Am J Med. 2012 Feb; 125(2): 183–189.

Important Bactrim Drug interactions

- Bactrim can cause hyperkalemia in pts prescribed ACE-I or ARBs or spironolactone
- Trimethoprim exhibits structural and pharmacologic similarities to the potassium-sparing diuretic amiloride
- reduces urinary potassium excretion by 40%
- Use cautiously in patients at risk for hyperkalemia

Arch Intern Med 2010 Jun 28;170(12):1045-9.

Case 2

64YM with history of epilepsy s/p VP shunt placement

- Admitted with septic shock and respiratory failure.
- PMH: h/o UTIs with ESBL E.coli
- YOU start Meropenem due to MDRO history
- Day 3 of admission, pt has a new seizure.

Admission Medication list:
- Citalopram
- Cyanocobalamin
- Divalproex acid
- Lamotrigine
- MVI

Case 2 Audience Response

What is the cause of the seizure?

a. Drug-drug interaction

b. VP shunt malfunction

c. Hypoxemic event

d. Propofol

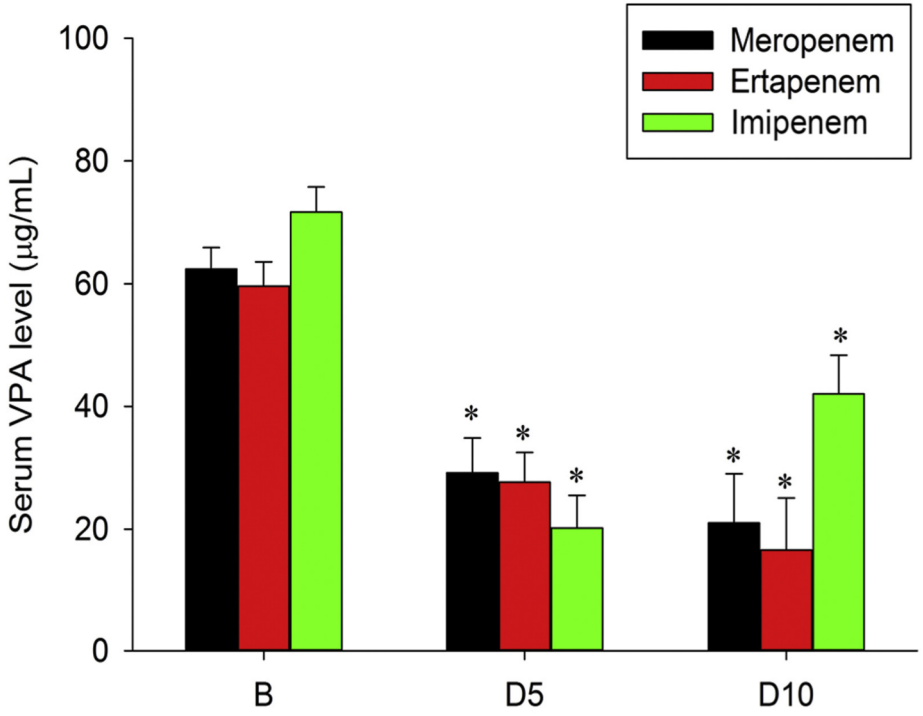
Did the carbapenem cause the seizure?

Carbapenem vs other abx	Odds Ratio, 95% CI
Carbs vs other abx	1.87 (1.35, 2.59)
Imipenem*	3.5 (2.23, 5.49)
Meropenem	1.04 (0.6, 1.77)
Ertapenem	1.32 (0.22,7.74)
Doripenem	0.44 (0.13, 1.53)

* Imipenem total daily dose, the Odds Ratio for patients receiving ≤2 and >2 g/day were 3.70 (95% CI 1.78, 7.69) and 4.85 (95% CI 2.61, 9.01), respectively

Cannon JP. 2014 Aug;69(8):2043-55

Carbapenems plus VPA = bad news



CR Huang 2017:33; 130-6.

Mechanism: enhances the glucuronidation of VPA, resulting in decreased serum levels of VPA

Reduces VPA levels by 52%- 78%

Onset within 24-48 hours

48% of patients experienced new seizure activity

Case 3:

57 y/o man with post-CABG sternal bone infection s/p several debridements is admitted to your hospital

Tissue culture from the first debridement +CoNS and viridans strep

Tissue culture from second debridement +CoNS

Pt was treated with vancomycin for 17 days, then switched to daptomycin 10 mg/kg daily d/t AKI and concern for SCr elevations with vancomycin

Upon routine monitoring in week 2, CPK rose for 98 to >3,000

Pt reported myalgias after directed questions.

Pt was also on atorvastatin

Case 3 Audience Response

What have daptomycin CK elevations been associated with?

a. Daptomycin trough levels

b. Statin use

c. Dose > 6 mg/kg

d. A & B

e. All of the above

Dose vs frequency

Administered at 6mg/kg in *S.aureus* bacteremia and endocarditis in phase III clinical trials:

- Higher rate of CPK elevations in dapto group vs comparator (6.7% vs 0.9%)
- 2.5% discontinued therapy to CPK elevations; returned to normal during or after daptomycin was dc'd
- Associated with trough level > 24.3 mg/L

Dose:

- VA study comparing standard vs medium (8 mg/kg) vs high dose (>/= 10mg/kg) : no difference in CPK elevations

Clin Infect Dis, 2017 Mar 1;64(5):605-613.
Clin Infect Dis, 2010 June 15; 50 (12):1568–1574

CPK elevations and statins

Among 3,042 patients:

- 4.2% had myopathy
  - CPK values elevated to >200 (>1 X ULN)
- 0.8% rhabdomyolysis
  - CPK elevations >2000 U/L (≥10 X ULN)
- Mean duration: 16.7 days

Risk Factor	Myopathy		Rhabdomyolysis	
	OR	*P* Value	OR	*P* Value
Age	0.99	.16	0.97	.05[a]
BMI >30 kg/m^2	1.48	.25	3.28	.03[a]
Cirrhosis	0.16	.10	…	…
Dialysis	0.39	.14	…	…
Cancer	0.55	.16	…	…
Bacteremia	1.28	.53	…	…
Osteomyelitis	1.74	.11	…	…
Deep abscess	2.80	.03[a]	…	…
Antihistamine coadministration	3.50	.03[a]	…	…
Statin coadministration	2.60	.03[a]	4.67	.03[a]

Abbreviations: BMI, body mass index; OR, odds ratio.
[a]Significant at $P \leq .05$.

Clin Infect Dis 2018 Oct 15;67(9):1356-1363.

Daptomycin pearls

- CK elevations are an uncommon occurrence, but recommend weekly monitoring of CK while on therapy
- Onset: symptoms associated with muscle toxicity typically appear after at least 7 days of therapy

Resolution:

- about 3 days after discontinuation

Discontinue when:

- unexplained signs and symptoms of myopathy together with increased CPK serum level to more than 1000 units/L
- in those without muscle pain but with CPK levels above 2000 units/L (10 times the normal upper limit)

Package insert: Daptomycin

Case 4

60F comes to your clinic with several months of dyspnea and cough and new fatigue. She denies any travel history or other illness except occasional UTIs. PMH: hypertension

Exam: dry crackles

LFTS elevated

Case 4 Audience Response

What UTI drug is associated with lung toxicity?

a. Bactrim
b. Fosfomycin
c. Doxycycline
d. Nitrofurantoin

Nitrofurantoin lung toxicity

Two flavors: Acute vs Chronic

Incidence: 1/100,000

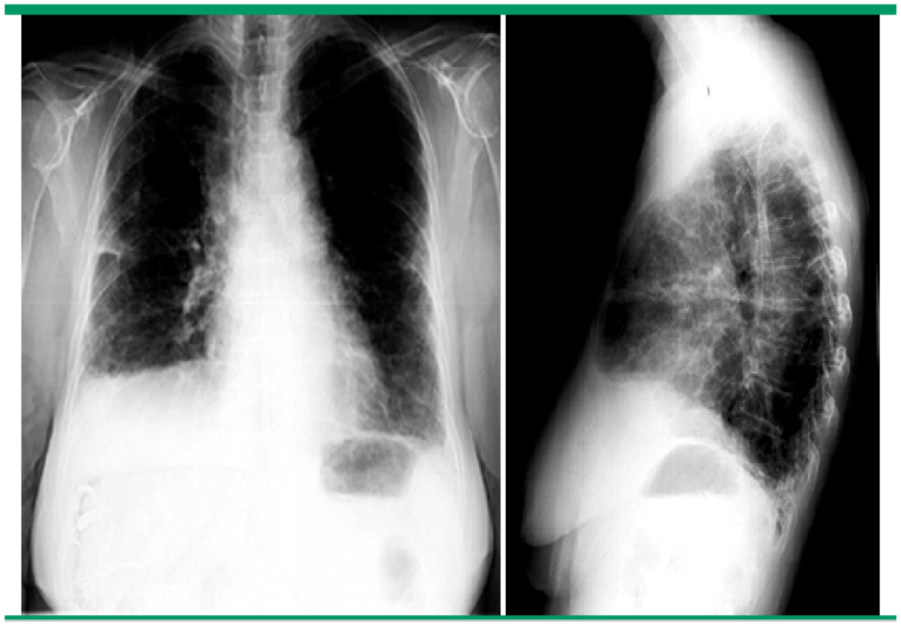
Acute:

- Onset: within hours to weeks of exposure
- SX: rapid onset of fever, cough, dyspnea, rash, and myalgia
- Peripheral Eosinophilia, LL infiltrates with/out pleural effusions
- Improvement occurs after DC of nitrofurantoin

NTF lung toxicity - Chronic

- Onset: months to years of exposure
- SX (most common): cough, dyspnea, chest pain, **elevated liver enzymes**
- Rarely: myalgias, wt loss, fatigue
- +/- FEVER
- Eosinophilia uncommon
- EXAM: Inspiratory crackles ("Velcro")
- CXR: bilateral interstitial infiltrates
- CT scan: bl ground-glass attenuation; no mediastinal /hilar adenopathy
- Some cases are irreversible

Nitrofurantoin-induced pulmonary injury



Posteroanterior and lateral chest radiographs show bilateral pleural effusions and parenchymal changes, predominantly located in the lower zones, in a 69-year-old woman who received nitrofurantoin for ten years because of recurrent urinary tract infections. Her symptoms consisted of dyspnea and a dry cough.

Courtesy of Justus de Zeeuw, MD.

UpToDate

Mayo Clin Proc 2005; 80:1298

Case 5

A 44 year old homeless man is sent to the ER from his methadone clinic with fever and cough.

PMH:

HIV+ with a CD4 =200, not on ARVs.

smokes 1 ppd cigarettes, does not drink

methadone maintenance X 5 years

His CXR shows a RUL infiltrate. AFB smear is positive.

He is admitted for treatment of pulmonary TB and started on RIPE. His methadone is continued.

Case 5 Audience Response

On his fifth hospital day he appears agitated and uncomfortable. He complains of abdominal pain, nausea, and diffuse muscle aches. VS essentially normal

ALT 55, AST 40.

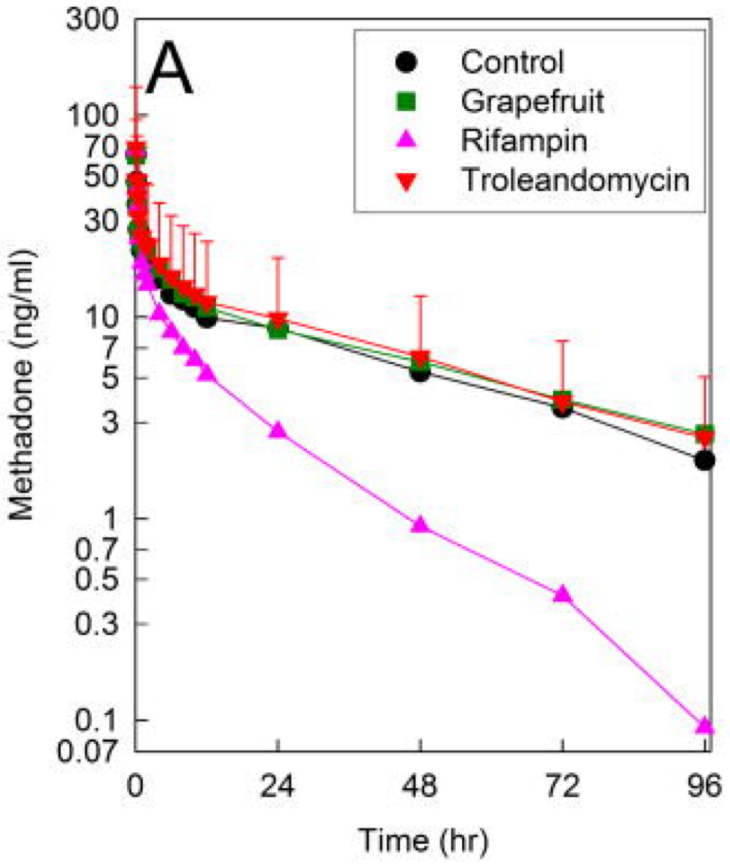
What is the most likely cause of his symptoms?

A. Rifampin hepatoxicity
B. INH hepatotoxicity
C. Opioid withdrawal
D. Immune Reconstitution Inflammatory Syndrome

Rifampin and Methadone

- Induction of P450 CYP3A4 by rifampin can decrease serum opioid levels by 30-65% and has been associated with appearance of withdrawal symptoms.

- Patients on methadone will likely require increased doses while on rifampin.
- Once TB treatment completed will need close monitoring to avoid sedation or overdose.



Clin Pharmacol Drug Dev. 2017 Mar; 6(2): 125–134

Case 6

65 year old female with a UTI was prescribed Bactrim. Three after starting therapy, she goes to the ED complaining of HA, neck pain and mental status changes.

HOD #4, patient is not improving: CSF cx are ngtd;

HSV & TB are pending

CSF = WBC: 200 cells/uL with neutrophil predominance; protein 100 mg/dL; glucose is normal

Case 6 Audience Response

What is the cause of her symptoms?

a. HSV

b. Syphilis

c. TB meningitis

d. Aseptic meningitis

Drug-induced aseptic meningitis

- Unusual Adverse Reaction
- Causes:
  - NSAIDS, TMP/SMX, IVIG, rofecoxib, cetuximab, anti-epileptic drugs and OKT3 antibodies
- Mechanisms:
  - Delayed type hypersensitivity reaction or direct meningeal irritation
- Treatment:
  - Stop drug; resolution within 2-3 days

Antibiotics ADRs are real!

Monitoring patients is key!
- have a routine monitoring plan in place for antibiotics

Resources for Antibiotic side effects:

- ✓PubMed
- ✓Colleagues!
- ✓Tertiary Resources
  - ✓UpToDate
  - ✓Mandell's Principles of Infectious Diseases
  - ✓Kucer's : The Use of Antibiotics
- ✓UWTASP

Clinical Infectious Diseases, Volume 68, Issue 1, 1 January 2019, Pages e1–e35, https://doi.org/10.1093/cid/ciy745