POTENTIAL HARMS OF ANTIBIOTIC USE

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CONFLICTS OF INTEREST

- No disclosures
GOALS AND OBJECTIVES

• Discuss adverse effects of common oral antibiotics
• Provide a healthy respect for potential harms of antibiotic use
• Discuss likelihood of above adverse effects
CAVEATS

• This is not all-encompassing
  • Focusing only on oral antibiotics
  • Looking at either common, under-recognized or rare, severe adverse effects

• For the most part, not getting into mechanisms of these reactions

• Will mostly cover antibiotics you might be prescribing
TOPICS

• Fluoroquinolones
• Azithromycin
• Tetracyclines (doxycycline, minocycline)
• TMP/SMX
• Clindamycin
• Metronidazole
• Linezolid
FLUOROQUINOLONES: THE GOOD

• Most common Examples:
  • Levofloxacin, Moxifloxacin, Ciprofloxacin

• Why do we use these?
  • Broad antimicrobial spectrum
  • Effective
  • Near 100% oral bioavailability
FLUOROQUINOLONES: THE BAD

- Resistance can develop quickly
- Black Box warnings:
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
- Additional adverse effects
  - QT prolongation/sudden cardiac death
  - Dysglycemia
FLUOROQUINOLONES: TENDINITIS/TENDON RUPTURE

- **Timing:** Median onset of 6 days
- **Incidence:** rare
  - 1/221 patients had tendinopathy; 1/832 had rupture
  - Risk: 4x risk of tendinitis, 2x risk of rupture
- **Location:** Most often Achilles
  - Can occur anywhere
- **Associated conditions**
  - Tendinitis - > 60 y/o, non-obese, on corticosteroids
  - Tendon rupture – women

Am J Med. 2012 December; 125 (12): 1228.e23-1228e28
FLUOROQUINOLONES: QT PROLONGATION

- Risk varies by agent
  - Moxifloxacin > levofloxacin > ciprofloxacín
- Lots of discrepancies among different studies
  - Variable designs and comparators
FLUOROQUINOLONES: QT PROLONGATION

Incidence of arrhythmias or cardiovascular death per 1000 individuals

- Ventricular arrhythmias
- Cardiovascular Deaths
- Arrhythmias or Deaths

- Amox/clav
- Ciprofloxacin
- Levofloxacin
- Moxifloxacin

Clin Infect Dis. 2015 Feb 15;60 (4): 566-77
FLUOROQUINOLONES: PERIPHERAL NEUROPATHY

• Key points:
  • Can be acute and rapid onset (days)
  • Risk appears unrelated to duration of therapy or age of patient
  • Can be permanent

• Estimated risk:
  • Total class effect - RR 1.83\textsuperscript{1}
  • ~2-3x risk for levofloxacin and ciprofloxacin\textsuperscript{1,2}
    • Moxifloxacin risk varied by study

1 - Neurology 83; Sept 30, 2014; 1261-1263
2 – Annals of Epidemiology 24; (2014) 279-285
**FLUOROQUINOLONES: DYSGLYCEMIA**

- **Key points:**
  - Mainly seen in diabetics
  - Associated with both hypoglycemia and hyperglycemia
  - Defined by ED visits or hospitalizations within 30 days of starting the antibiotics

![Graph showing adjusted OR for hypoglycemia and hyperglycemia with different fluoroquinolones]
**FLUOROQUINOLONES: SUMMARY**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tendinopathy</th>
<th>QT Prolongation</th>
<th>Peripheral Neuropathy</th>
<th>Dysglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Levofloxacin</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
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</tbody>
</table>

2016: FDA statement advising that FQs should be reserved for conditions where there are not other options due to potentially permanent, disabling adverse effects.
FLUOROQUINOLONES: TAKE HOME POINTS

• FQs have a lot of potential for severe AE including tendon rupture, sudden cardiac death, peripheral neuropathy, and dysglycemia

• While the absolute risk of these is low, they can have rapid onset, be permanent, and associated with significant morbidity

• Use when appropriate, with appropriate caution
You have a 57 y/o female with depression, CAD s/p MI, and atrial fibrillation who comes to the hospital with community acquired pneumonia. Medications include fluoxetine, trazodone, metoprolol, ASA, and amiodarone. What guideline-recommended regimen could you use to limit toxicity in this patient?

- A. Levofloxacin
- B. Moxifloxacin
- C. Ceftriaxone + doxycycline
- D. Ceftriaxone + azithromycin
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AZITHROMYCIN

- Cardiac toxicity

Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.
AZITHROMYCIN

- Almost 3x Increased risk of cardiac death (HR 2.88, 1.79-4.63)
  - 47 deaths per 1 million courses
  - 245 deaths per 1 million courses for high-risk

![Graph showing excess deaths in different risk categories for Azithromycin and Amoxicillin.](image)
AZITHROMYCIN

• Several additional studies have looked at this with somewhat discrepant results

• The overall take home:
  • Although there are some mixed data out there, Azithromycin is likely associated with a slight increase in cardiovascular death and this effect is significantly increased in people with cardiac comorbidities
63 y/o with history of an MRSA prosthetic joint infection (PJI) who is currently receiving chronic, life-long suppressive therapy for this MRSA PJI. She comes in for her yearly follow up after 2 years of therapy with the skin changes seen below. What antibiotic was she on for her PJI?

A. TMP/SMX
B. Linezolid
C. Minocycline
D. Doxycycline
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B. Linezolid
C. Minocycline
D. Doxycycline
TETRACYCLINES

- Minocycline
  - Skin hyperpigmentation
  - Drug-induced lupus
- Doxycycline
  - Skin hypersensitivity
  - Esophagitis
TETRACYCLINES

- Minocycline
  - Skin hyperpigmentation
    - Requires long-term exposure (usually 6-12 months)
    - Occurs in up to 40% of patients on extended courses

The Journal of Rheumatology 2006; 33:7; 1254-1257
TETRACYCLINES

• Minocycline: Drug-induced lupus
  • Symptoms: malaise, myalgias, arthralgias, arthritis
  • Almost exclusively in women (88%)
  • Improves with discontinuation
    • Usually recurs with re-exposure
  • Absolute risk: 1 in 1000
  • Lab findings
    • Positive ANA, ds-DNA, ANCA found in 92-93%
    • Anti-histone Ab uncommon

1. Arch Dermatol (Oct 1997); Vol 133; 1224-1230
TETRACYCLINES

• Doxycycline
  • Skin hypersensitivity
    • Relatively common: up to 8% of patients
    • Does not require extensive sun exposure
TETRACYCLINES

- Doxycycline

  - Esophagitis
    - Often young or middle-aged women
    - History of swallowing capsule with small amounts of water or in recumbent position

  - Symptoms
    - Dysphagia, odynophagia, or retrosternal pain
TETRACYCLINES: TAKE HOME POINTS

• When using minocycline chronically (ie for acne), be aware of skin hyperpigmentation and drug-induced lupus. Avoid use in patients with lupus.

• When prescribing doxycycline, recommend avoidance of sun exposure and/or use strong sun protection.

• In addition, it is important to counsel patient to take with 8oz of water and remain upright for 30 minutes after taking the pill.
73 y/o male with HTN and mild CKD with baseline creatinine of 1.3 comes in for follow up of MRSA prosthetic joint infection currently on lifelong suppressive therapy with doxycycline. He is having trouble tolerating this and is switched to TMP/SMX. Follow up creatinine in 1 week is 1.6, potassium 4.4. What is the most appropriate next step?

1. Discontinue TMP/SMX and start linezolid
2. Discontinue TMP/SMX and start cephalexin
3. Discontinue TMP/SMX
4. Recheck labs in 3-5 days
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TRIMETHOPRIM/SULFAMETHOXAZOLE

- Renal effects
  - True acute kidney injury is rare (AIN)
  - Does ‘artificially’ increase creatinine
    - Decreases tubular secretion of creatinine
    - Causes increase in creatinine without affecting GFR

65 y/o with h/o MRSA prosthetic joint infection on suppressive therapy with chronic TMP/SMX. Her BP today is 155/90 and home BP monitoring shows similar readings. Along with lifestyle changes you want to start a medication for her HTN. What medication should you avoid if possible?

1. HCTZ
2. Lisinopril
3. Amlodipine
4. Chlorthalidone
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TRIMETHOPRIM/SULFAMETHOXAZOLE

• Hyperkalemia
  • Sudden death reported with concurrent spironolactone, ACEI, or ARB
    • Increases risk of sudden death by ~50%
    • 3 sudden deaths per 1000 prescriptions
  • Usually seen with higher doses but can occur with normal dosing
  • Associated with increased hospitalizations for hyperkalemia
    • 6-20% of patients have K >5.4
TRIMETHOPRIM/SULFAMETHOXAZOLE

• Potentially severe reactions (worse in elderly)
  • Neutropenia
  • Anaphylaxis
  • Severe dermatologic reactions – SJS, TEN, etc

• Other reactions
  • Hemolysis, hyponatremia, hypoglycemia, hepatitis, RTA
TRIMETHOPRIM/SULFAMETHOXAZOLE

• Take home points:
  • AKI is rare but ‘artificial’ mild Cr elevation is common
  • Be cautious using with other K+ increasing meds
    • Not contraindicated, just warrants monitoring
  • TMP/SMX can have be associated with a wide variety of adverse effects so monitor closely with high doses or prolonged courses
43 y/o with a history of recurrent *C diff* infections comes in with cellulitis. What antibiotic used for non-purulent cellulitis would have the highest risk for predisposing to *C diff*?

1. Cephalexin
2. Amox/clav
3. Clindamycin
4. Levofloxacin
• 43 y/o with a history of recurrent C diff infections comes in with cellulitis. What antibiotic used for non-purulent cellulitis would have the highest risk for predisposing to C diff?

• 1. Cephalexin
• 2. Amox/clav
• 3. Clindamycin
• 4. Levofloxacin
CLINDAMYCIN

- Highest risk of C diff
  - Initial study showed OR of 16.8

FIG 3 Linear association between a 4-point antibiotic risk index and community-associated CDI risks.
**Antimicrobial agents that may induce *Clostridium difficile* diarrhea and colitis**

<table>
<thead>
<tr>
<th>Frequently associated</th>
<th>Occasionally associated</th>
<th>Rarely associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Macrolides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Cephalosporins (broad spectrum)</td>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Graphic 55479 Version 5.0

NAME THE ANTIBIOTIC:

- 58 y/o male with cryptogenic cirrhosis is being admitted to the hospital after a fall. Prior to the fall he had been on an antibiotic for the past 3-4 weeks. A few days prior to the admission he developed dysarthria and gait instability. MRI is pictured:

- What antimicrobial was he on?
  - A. Amoxicillin
  - B. Isoniazid
  - C. Fluconazole
  - D. Metronidazole
NAME THE ANTIBIOTIC:

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  • C. Fluconazole
  • D. Metronidazole
METRONIDAZOLE

• Notable adverse effects
  • Neurologic effects
    • Peripheral neuropathy
    • Seizures
    • Encephalopathy

• Key features
  • Often based on cumulative dosing
METRONIDAZOLE: NEUROLOGIC EFFECTS

• Peripheral neuropathy
  • Studied for use with drug-resistant TB
  • At cumulative dose of 90g, 50% of patients had neuropathy
    • Low risk at <42g total dose
  • Mostly reversible but can take a long time
    • Median of 1006 days after therapy
  • Thought to be cumulative, even across time

Antimicrobial Agents and Chemotherapy (Aug 2013); 57 (8); 3903-3909
Annals of Epidemiology 24; (2014) 279-285
METRONIDAZOLE: NEUROLOGIC EFFECTS

• Encephalopathy
  • Dysarthria, gait instability
  • Affects Cerebellum
  • Somewhat reversible, some deficits often remain
  • Based on cumulative dosing, usually > 20g (2 week course)

• Seizures
  • Associated with cumulative doses > 40g
METRONIDAZOLE: TAKE HOME POINTS

- Be careful with prolonged or repeated exposures
  - Peripheral and central nervous system effects
    - Peripheral neuropathy, dysarthria, ataxia, seizures
    - Can have permanent or long-lasting effects
37 y/o female with h/o depression and IVDA comes in with MRSA pneumonia. Her other medications include sertraline and trazodone. You want to start oral linezolid. According to the FDA, what should you do with her other medications?

1. No adjustment necessary
2. Discontinue sertraline and trazodone immediately
3. Halve the doses of sertraline and trazodone
4. Start a taper of sertraline and trazodone
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LINEZOLID

• Serotonin Syndrome
  • Linezolid is a MAOI inhibitor
  • FDA warning

<table>
<thead>
<tr>
<th>Urgency</th>
<th>FDA Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent</td>
<td>Immediate discontinuation of SNRI or SSRI</td>
</tr>
<tr>
<td>Non-Emergent</td>
<td>Stop SSRI/SNRI 2 weeks before starting linezolid</td>
</tr>
</tbody>
</table>
LINEZOLID: SEROTONIN SYNDROME

• Real-world risk
  • Overall very low incidence, even with co-administration
    • One study showed 1/87 patients with co-admin met strict criteria
    • One study looking at 2208 patients showed only 0.14% met Hunter Serotonin Toxicity Syndrome
  • Appears to increase risk of serotonin syndrome 3-fold when co-administered but absolute risk is low and studies have failed to show statistical significance
LINEZOLID: SEROTONIN SYNDROME

• Recognizing serotonin syndrome
  • Mental status changes
  • Autonomic hyperactivity
  • Neuromuscular abnormalities

• Onset
  • Usually within 24 hours of medication change

• Severity
  • Can be life threatening

Figure 1.
Hunter's decision rules for diagnosis of serotonin toxicity.
LINEZOLID

• Bone marrow suppression
  • Usually seen with courses > 2 weeks
  • Thrombocytopenia > anemia, no sig effect on WBC
    • Mild and reversible

• Peripheral neuropathy
  • Can be severe and permanent
  • Usually seen with courses > 28 days
LINEZOLID

- Take home points:
  - Use of linezolid is currently limited given concern for serotonin syndrome when used with other serotonergic medications
  - Studies are showing that these events are rare, even with co-administration
  - Risk/benefit of use of linezolid needs to be weighed for each individual patient on serotonergic medications
LINEZOLID

• Take home points:
  • Linezolid suppressed bone marrow and monitoring for platelets and Hgb is recommended for courses > 2 weeks
    • These effects are often mild and reversible
  • For prolonged courses (ie >28 days), permanent peripheral neuropathy does occur
    • FDA limits recommended courses to 28 days
SUMMARY

- While fluoroquinolones are effective antibiotics, they have several potentially severe, permanent adverse effects that are associated with them and appropriate caution should be used.
- Use azithromycin with caution in patients with cardiac comorbidities.
- Be aware of potential AE with long-term use of minocycline including skin hyperpigmentation (common) and drug-induced lupus (rare).
SUMMARY

• Counsel patients using doxycycline about skin hypersensitivity and esophagitis

• TMP/SMX rarely causes AKI but should be used with caution in patients on other potassium raising medications (ACEI/ARB, spironolactone, etc)

• Different classes of antibiotics are associated with different risks of C diff
  • Clindamycsin is highest, doxycycline lowest
SUMMARY

• Metronidazole-associated adverse effects are often based on cumulative dosing and include peripheral neuropathy, seizures, and encephalopathy

• Linezolid has been associated with slightly increased risk of serotonin syndrome and should be used with caution in those on other serotonergic medications