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Seattle
October 31, 2019
Antibiotics in 2019: Disclosures, Objective, Scope

Disclosures
• No financial conflicts of interest
• Lots of off-label use… will call it out

Objective
• Increase your comfort & skill prescribing anti-infectives

Scope
• Hospitalist / Inpatient Consult
Antibiotics in 2019: Stewardship Opportunities

- Fluoroquinolones
  - Good, Bad… Ugly
  - Alternatives

- Antibiotic Allergies
  - Aggravating Realities…
  - Exciting opportunities…

- Multi-Drug Resistant Org’s
  - Update in WA
  - New Treatment Options

- C.difficile Infection
  - Treatment Update
  - Prevention Strategies

- Pearls by P-Squared
Fluoroquinolones: *The Good*

**Broad Spectrum…**
- GNR coverage!
- GPC coverage!

**Easy to use…**
- Once or Twice Daily!
- IV to PO conversion is a snap!
- Multiple flavors to choose from!
Fluoroquinolones: *The Bad*

Broad Spectrum…

*Not what it used to be*

<table>
<thead>
<tr>
<th>Levofloxacin Susceptibility</th>
<th>UW Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep pneumoniae</td>
<td>97%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>75%</td>
</tr>
<tr>
<td>E.coli</td>
<td>66%</td>
</tr>
<tr>
<td>MRSA</td>
<td>17%</td>
</tr>
</tbody>
</table>
Fluoroquinolones: The Ugly

- Antibiotic-Associated Diarrhea / C. difficile
- Tendonitis / Tendon Rupture
- Hypoglycemic coma (or hyperglycemia!)
- QTc Prolongation
- Photosensitivity
- Myesthenia Gravis Crisis
- Delirium / Psychosis
- Peripheral Neuropathy
- Aortic Rupture
FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on May 12, 2016.
Tendinitis Risk: 2.4 / 10,000

Tendon Injury Risk Factors
- Advanced Age
- Male Gender
- Low GFR
- Rheumatologic Dz
- Corticosteroid use
- Hyperlipidemia
- Hyperparathyroidism
- Physical Activity

ATR Risk: 1.2 / 10,000
“We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.”

–FDA, 5/12/16
FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients

This information is an update to the FDA announcement issued on May 10, 2017

Safety Announcement

[12-20-2018] A U.S. Food and Drug Administration (FDA) review found that fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta. These tears, called aortic dissections, or ruptures of an aortic aneurysm can lead to dangerous bleeding or even death. They can occur with fluoroquinolones for systemic use given by mouth or through an injection.

https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm
Fluoroquinolones: Concern for Aortic Injury

Lee CC JAMA Int Med 2015 (N=1,477)
• Aortic rupture rate ratio 2.28 (95% CI=1.67-3.13) after adjustment.
• Age > 70 highest risk factor.
• FDA: “significant design and analytical limitations with the study.”

Daneman N BMJ Open 2015 (N=657,950)
• Retrospective cohort: rupture ≥ 65 y/o first 30 days FQ vs no FQ
• 2.24-fold increased risk (95% CI=2.02-2.49)
• FQ pts more likely to have RF’s (HTN, DM, ASCVD)

Pasternak B BMJ 2018 (N=360,088)
• Retrospective cohort: rupture ≥ 50 y/o first 60 days FQ vs amox
• 1.66-fold increased risk (95% CI=1.12-2.46) vs amox
• Greatest risk first 10 days… no increased risk day 61-120.

Lee CC JACC 2018 (N=1,213)
• Self-controlled analysis: elderly pts 60 days before rupture vs random other time
• FQ exposure OR=2.71 (95% CI=1.14-6.46)
• 3-14 days OR=2.41 (95% CI=1.25-4.65); for >14 days OR=2.83 (95% CI=1.06-7.57)

FDA 2018
• 56 “additional” cases of aortic rupture 2015-2017, most from malpractice lawsuits.
• All cases had at least one risk factor for rupture.
“Health care professionals should avoid prescribing FQ antibiotics to patients who have an aortic aneurysm or are at risk, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions… and elderly patients. Prescribe FQs to these patients only when no other treatment options are available. Advise all patients to seek immediate medical treatment for any symptoms associated with aortic aneurysm. Stop FQ treatment immediately if a patient reports side effects suggestive of aortic aneurysm or dissection.”

–FDA, 12/20/18
Heightened FQ Concern: Aortic Rupture

- Medicolegal implications
- Patient information: FDA Fact Sheet a starting point...

https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm

Fluoroquinolones: Threats... Opportunities

- Additional Information for Patients
  - Fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta. These tears, called aortic dissections, or ruptures of an aortic aneurysm can lead to dangerous bleeding or even death.
  - People at risk for aortic aneurysms include those with a history of blockages or aneurysms of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes such as Marfan syndrome and Ehlers-Danlos syndrome, and the elderly.
  - FDA is requiring that a new warning about the rare but serious risk of aortic aneurysm be added to the prescribing information and patient Medication Guide of all fluoroquinolone antibiotics.
  - Seek medical attention immediately by going to an emergency room or calling 911 if you experience sudden, severe, and constant stomach, chest or back pain.
  - Imaging tests are used to diagnose an aortic aneurysm. If you have a history of aneurysms, routine checkups and treatment for an aortic aneurysm can help prevent growth and rupture.
  - If you have an aneurysm, signs and symptoms of a growing aortic aneurysm depend on its location along the aorta blood vessel and can include:
    - A throbbing feeling in the stomach area
    - Deep pain in your back or the side of your stomach area
    - Steady, growing pain in your stomach area that lasts for hours or days
    - Pain in your jaw, neck, back or chest
    - Coughing or hoarseness
    - Shortness of breath, and trouble breathing or swallowing
  - Contact your health care professional immediately if you experience any serious side effects while you are taking your fluoroquinolone antibiotic.
  - Before starting a new fluoroquinolone antibiotic, inform your health care professional if you have previously experienced any serious side effects with another antibiotic.
  - Lifestyle changes can help lower the risk of developing an aortic aneurysm. These include:
    - Stopping smoking. The health benefits of quitting smoking are immediate and substantial. Soon after quitting, circulation and blood pressure improve, the senses of taste and smell return, and it becomes easier to breathe. In the longer term, quitting smoking can decrease the chances of developing lung disease, heart disease, and some cancers. More information about quitting smoking can be found on the National Cancer Institute's website and the Smokefree website.
    - Healthy diet. A healthy diet is low in saturated fat, trans fat, cholesterol, salt, and added sugar. More information about following a healthy diet can be found on the National Heart, Lung, and Blood Institute’s website.
    - Controlling medical conditions such as high blood pressure and high blood cholesterol.
  - Read the patient Medication Guide you receive with your fluoroquinolone antibiotic prescriptions, which explains the important things you need to know about the medicine. These include side effects, what the medicine is used for, how to take and store it properly, and other things to watch for when you’re taking the medicine.
  - Talk to your health care professional if you have questions or concerns about fluoroquinolone antibiotics.
Fluoroquinolone Alternatives: Cystitis

- Nitrofurantoin (*Macrobid*) 100mg PO BID x 5 days (caution in pyelo, GFR<30, age> 65) OR
- TMP/SMX (*Bactrim*) resistance <20%:
  - 1 DS PO BID x 3 days OR
- Fosfomycin (*Monurol*) 3gm PO x 1 dose (not for pyelo!)
- TMP/SMX resistance >20%:
  - Cipro 500mg PO QD x 3 days OR
  - Cefpodoxime 100mg PO BID x 7 days OR

Do you know local E.coli resistance? Modified IDSA recommendations soon?
Ambulatory

**COPD Exacerbation**

- **Amox-Clav 875mg PO BID or 500mg PO TID x 5 D**
- **Amox 500mg PO TID x 3-14 D**
- **Doxy 100mg PO BID x 3-14 D**
- **Cefuroxime 500mg PO BID x 10 D**
- **Azithro 500mg PO x 1 then 250mg PO QD x 4 D**
- **Levo or Moxi x 5 days**

- **Dyspnea?**
- **Increased sputum?**
- **More purulent sputum?**

- ✓ Abx if all 3 present
- ✓ Abx if purulent sputum plus 1 other
- ✓ Abx if admitted and ventilated

Fluoroquinolone Alternatives: **ABECB**

**COPD Exacerbation**

- ✓ Abx if all 3 present
- ✓ Abx if purulent sputum plus 1 other
- ✓ Abx if admitted and ventilated

**Admitted**

Treat as for CAP

(Ceftriaxone + [azithro or doxy]) x 5 D
Fluoroquinolone Alternatives: Sinusitis

1st Line Empiric Abx
• Amox-Clav 875-2000 mg PO BID x 5-7 Days

2nd Line Empiric Abx
• Doxycycline 100 BID or
• Levofloxacin 500 QD or
• Moxifloxacin 400 QD

No Longer Recommended
• Azithromycin, TMP/SMX

Modified IDSA recommendations soon?

2012 IDSA Guidelines
USA Prescriptions in 2014

- FQ Courses: 31.5 Million
- Abx not indicated at all: 5%
- FQ not first-line indication: 20%

Use 2012-2017 dropped by 10% per year

Fluoroquinolones: Heavy Use

<table>
<thead>
<tr>
<th>Indication</th>
<th>% FQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>49%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>40%</td>
</tr>
<tr>
<td>SSTI</td>
<td>26%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
</tr>
<tr>
<td>URI</td>
<td>11%</td>
</tr>
</tbody>
</table>
Antibiotic Allergies: A Hot Mess

“I’m allergic to penicillin”

- 10% of Americans report a “penicillin allergy”
- > 90% of these are bogus! (nausea, yeast infxn....)
- Beta-lactams are generally safe, effective, well-tolerated
- 50% increase in surgical site infections and adverse reactions with second-line abx (vanco alone, clinda, FQ)

Blumenthal Clin Infect Dis 2018
Antibiotic Allergies: *Opportunity!*

**History** is key: “Talk more, test less!”

- **WHAT?** (Airway? Intubation? Itching? “Hives” used differently by folks)
- **WHEN?** (Relation to dose? >10 years ago?)
- **WHO?** (Witnessed, recorded, historical?)
- Beware shibboleths in the **EMR**!
- Patient need elective surgery? Often on abx? You have time to **get this right!**
- Start thinking about abx allergies **before** they are needed
Antibiotic Allergies: *Options*

- > 1 Year Ago
  - Benign Rash
  - GI upset
  - Other benign issue
  - Unknown Hx

**Oral amoxicillin challenge**
(very safe, > 95% have no reaction!)

- Within last year
- Airway / Anaphylaxis
- Pt or Provider Preference

**Skin Testing**

*Histamine, Saline, Penicillin*
**Klebsiella pneumoniae Carbapenemases**

- Enzymes hydrolyze carbapenems
- All Carbapenems affected
- *Klebsiella pneumoniae* strongest association… also seen in other *Enterobacteriaceae* & *P. aeruginosa*
- Usually transferred on plasmids
- Part of broader group: Carbapenem-Resistant Enterobacteriaceae (CRE)
Epidemiological Risk Factors

- Recent hospitalization
- SNF, LTAC, etc
- Healthcare overseas (medical tourism)
- Tremendous numbers of clinical and environmental isolates from India are positive for carbapenem-resistant enterobacteriaceae (CRE).
- KPC reported in every state.
MDR Gram-Negative Rods: New Drugs

New KPC Treatment Options

• Ceftolozane-Tazobactam (Zerbaxa) anti-Pseudomonas with some ESBL activity

• Ceftazidime-Avibactam (Avycaz) anti-ESBL / KPC with novel BLI

• Meropenem-Vaborbactam (Vabomere) anti-ESBL / KPC with novel BLI

• Imipenem-Relebactam (not yet approved) anti-ESBL / KPC with novel BLI
Traditional BLIs
(tazobactam, sulbactam, clavulanate)

New non-BL BLIs
(avanibactam, vaborbactam, relebactam)
MDR Gram-Negative Rods: New Drugs

New Treatment Options

• Ceftolozane-Tazobactam (Zerbaxa)
  $243 / day

• Ceftazidime-Avibactam (Avycaz)
  $840 / day

• Meropenem-Vaborbactam (Vabomere)
  $460 / day

• Imipenem-Relebactam (not yet approved)
  $? / day

✓ All are IV
✓ All are expensive
✓ All have gaps in coverage
✓ Resistance may emerge on therapy
Patients with **NDM-producing Carbapenem-resistant Enterobacteriaceae (CRE)** reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state

New BL/BLI’s: **NOT** reliable in NDM CRE
MRSA Reality: One Common Foe

Community-Associated MRSA  Healthcare-Associated MRSA
MDR Gram-Positives: New Anti-MRSA Drugs

- **Dalbavancin** (Dalvance)
  - Class: Lipoglycopeptide
  - Indication: gram-positive ABSSSI
  - 1.5 gm IV x 1 or 1 gm then 500 mg day 7; “$4,500 / course”
  - May elevate LFTs; dose reduce in severe liver dysfunction

- **Oritavancin** (Orbactiv)
  - Class: Lipoglycopeptide
  - Indication: gram-positive ABSSSI
  - 1.2 gm IV x 1; “$3000 / course”
  - Falsely elevates aPTT x 5 days post-infusion
## MRSA Susceptibility: Seattle 2019

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>HMC (44% S.aureus)</th>
<th>UWMC (31% S.aureus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>55%</td>
<td>49%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>83%</td>
<td>89%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
MDR Gram-Positives: **PWID Population**

- **Persons who Inject Drugs**
  - MRSA complications: BSI, IE, SEA, osteomyelitis…
  - Concern: IV access, LOS, oral abx compliance
  - Issue: These are off-label indications for dalba & orita

- Setting: Harborview Medical Center (public safety-net hospital)
- Retrospective: 32 PWID complicated ID (BSI, IE, SEA, STP)
- Treatment: Average 13 days standard abx, then dalbavancin

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average LOS</td>
<td>12 ± 8.5 days</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>18 (56%)</td>
</tr>
<tr>
<td>Clinical Failure</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Lost to Followup</td>
<td>10 (31%)</td>
</tr>
</tbody>
</table>
Antibiotics in 2019: Often a Source of Badness

Antibiotic Complications are Common

- 1488 adult hospitalized pts
- Retrospective chart review at 90 days
- **298 (20%)** had adverse event
- Diarrhea, heme disorders, renal injury, allergic reaction…
- 19% had no indication for abx given

*Your Judicious Use Matters!*
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald, 1 Dale N. Gerding, 2 Stuart Johnson, 23 Johan S. Bakken, 4 Karen C. Carroll, 5 Susan E. Coffin, 6 Erik R. Dubberke, 7 Kevin W. Garey, 9 Carolyn V. Gould, 1 Ciaran Kelly, 9 Vivian Loo, 10 Julia Shaklee Sammons, 6 Thomas J. Sandora, 11 and Mark H. Wilcox 12

1Centers for Disease Control and Prevention, Atlanta, Georgia; 2Edward Hines Jr Veterans Administration Hospital, Hines, and 3Loyola University Medical Center, Maywood, Illinois; 4St Luke's Hospital, Duluth, Minnesota; 5Johns Hopkins University School of Medicine, Baltimore, Maryland; 6Children's Hospital of Philadelphia, Pennsylvania; 7Washington University School of Medicine, St Louis, Missouri; 8University of Houston College of Pharmacy, Texas; 9Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; 10McGill University Health Centre, McGill University, Montréal, Québec, Canada; 11Boston Children's Hospital, Massachusetts; and 12Leeds Teaching Hospitals NHS Trust, United Kingdom
C. difficile Infection: Treatment Recommendations

<table>
<thead>
<tr>
<th>Initial Episode, Not Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Vanco 125mg PO Q 6 H x 10 days</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>✓ Fidaxomicin 200mg PO BID x 10 days</td>
</tr>
<tr>
<td>OR, only if neither available…</td>
</tr>
<tr>
<td>✓ Metronidazole 500mg PO TID x 10 days</td>
</tr>
</tbody>
</table>

**Initial Episode, non-severe**
- Leukocytosis with a white blood cell count of ≥15,000 cells/mL and a serum creatinine level < 1.5 mg/dL

**Initial episode, severe**
- Leukocytosis with a white blood cell count of ≥15,000 cells/mL or a serum creatinine level > 1.5 mg/dL

**Initial episode, fulminant**
- Hypotension or shock, ileus, megacolon

**First recurrence**
- VAN 125 mg twice daily for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR
- FDX 200 mg given twice daily for 10 days, OR
- Fecal microbiota transplantation

**Second or subsequent recurrence**
- VAN in cases of resistance to VAN, only if neither available…

**Clinical Definition**
- Leukocytosis with a white blood cell count of ≥15,000 cells/mL and a serum creatinine level < 1.5 mg/dL

**Supportive Clinical Data**
- VAN 125 mg PO Q 6 H x 10 days
- FDX 200 mg PO BID x 10 days
- Metronidazole 500 mg PO TID x 10 days

**Abbreviations:** FDX, fidaxomicin; VAN, vancomycin.

1. All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

2. The criteria proposed for defining severe or fulminant Clostridium difficile infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

3. The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.
“Newer sometimes better”

- Macrocyclic antibiotic
- Not absorbed from gut
- Narrower spectrum than metronidazole… gentler on beneficial GI commensals

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fidax  (n=287)</th>
<th>Vanco (n=309)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-week Recurrence</td>
<td>15.4%</td>
<td>25.3%</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Global Cure</td>
<td>74.6%</td>
<td>64.1%</td>
<td>p=0.006</td>
</tr>
<tr>
<td>Global Cure B1/NAP1</td>
<td>78.7%</td>
<td>80.7%</td>
<td>p=NS</td>
</tr>
</tbody>
</table>

Louie *NEJM* 2011
C. difficile Infection: **Fidaxomycin (Dificid)**

Retail Cost: **$3800 for 10 days.**

Coupon program online may help...
C. difficile Infection: *Oral Vancomycin (Firvanq)*

“Old school is new again”

- Same antibiotic you give IV
- Not absorbed from gut
- Also narrower spectrum than metronidazole… gentler on beneficial commensals
- Oral tabs (“pulvules”) have been very expensive
- Liquid compounding kits
  - FDA approved January 2018
  - Driving down cost of pills! Equally effective
Fecal Microbiota Transplant

• The Ultimate Pro-Biotic experience!
• ~ 90% cure rate in case series and reports
• Small N’s to date
• Patients much less squeamish than MDs
• Unresolved Issues:
  ✓ Donor selection & screening
  ✓ Stool Prep & Delivery
  ✓ Reimbursement
  ✓ Operationalize as inpatient?

Bakken Clin Gastro Hepatol 2011
Antibiotics Pearls: IV... or PO?

- IV route **NOT** required for insurance reimbursement
- Convert to PO based on your clinical judgment, not fear of CMS!
Antibiotics Pearls: *Urine Culture = TMI?*

- Urine culture **NOT** required pre-op (unless urinary surgery).
- Considering CA-UTI? Consider UA first, then culture if convincingly positive ("reflexive" culture).
- You can depend on:
  1. Death
  2. Taxes
  3. **Positive Foley urine culture**
Antibiotics Pearls: *Sin of Vanc + Zosyn?*

- Seductive... may be nephrotoxic... often overkill.
- Do you really need to cover Staph, plus most Pseudomonas, plus all anaerobes?
- May be quite reasonable empirically:
  1. Complicated HA-intraabdominal infxn
  2. Fournier’s Gangrene
Antibiotics Pearls: Sepsis is Deadly Serious

• Thank you for being careful with abx!
• Got sepsis? Please respond rapidly... test... resuscitate... and treat aggressively with abx
• Totally fine to change—or stop—abx after 24-72 hours, based on your workup. “Change is Good.”
Antibiotics in 2019: Conclusions

- Fluoroquinolones: Know the risks... Know the alternatives
- Antibiotic Allergies: Often bogus, Usually easy to fix!
- MDR GNRs: New treatments... but get help from ID!
- MDR GPCs: Older drugs often fine...
- Got C.diff? Just say “Vancomycin!”
- No preop orthopedic urine workup if asymptomatic
- Vo-Syn may be fine... just consider alternatives
- Sepsis = emergency... use abx, and quickly!
- Your current practice already excellent...

Truly... Thank You