

5 February, 2019

## Agenda

- Paul Pottinger: *Fluoroquinolone Toxicity: Big Bowl of Bad*
- Case Discussions
- Open Discussion



# UW/TASP

tele-antimicrobial stewardship program



Paul Pottinger MD

- No financial conflicts of interest.
- Everything we discuss is QI, thus protected from legal discovery under WA State Code.

# 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....*



- Spectrum not what it used to be

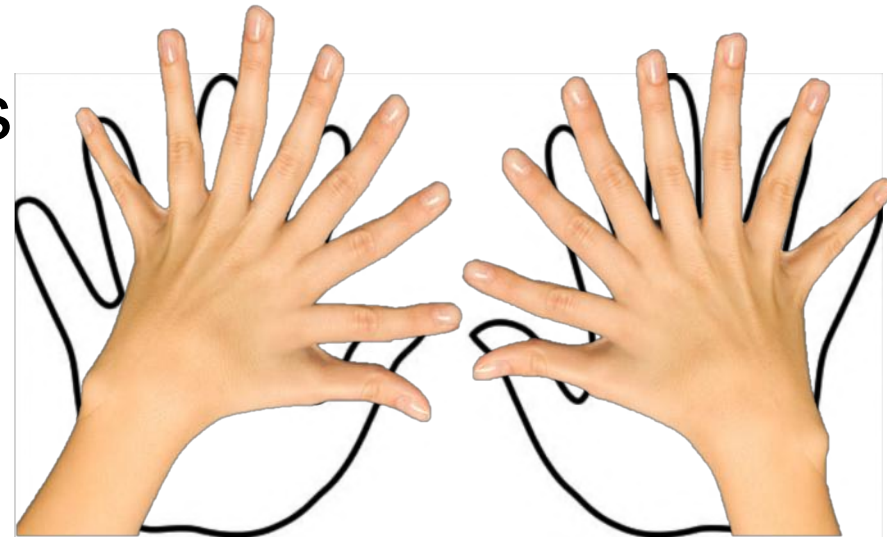
Levofloxacin Susceptibility UW Medicine	
Strep pneumoniae	97%
P. aeruginosa	75%
E.coli	66%
MRSA	17%



# Fluoroquinolones: *The Ugly....*



- Antibiotic-Associated Diarrhea / C.difficile
- Tendonitis / Tendon Rupture
- Dysglycemia (high or low!)
- QTc Prolongation (cardiac arrhythmia)
- Photosensitivity
- Myasthenia Gravis Crisis
- Delirium
- Peripheral Neuropathy
- Lens Dislocation
- Aortic Rupture



# Heightened FQ Concern: *Neuropathy*

## HURT BY LEVAQUIN

BRAIN/BODY TOXIC DRUG

[HOME](#)[BLOG](#)[PURPOSE OF BLOG](#)[SIDE EFFECTS](#)[MEDIA/NEWS](#)[REFERENCES](#)[LINKS](#)[ADVOCACY](#)[JOHNSON & JOHNSON](#)

## HURT BY LEVAQUIN



### *Welcome to My Website*

*After suffering through approximately three years of daily pain from an antibiotic called Levaquin, I decided to begin documenting my life in an effort to help educate the public.*



LIFE BEFORE  
LEVAQUIN

*If I can save just one person from having their life ruined as a result of Levaquin toxicity, then this blog will have served its*

*purpose.*

[www.levaquinadversesideeffect.com](http://www.levaquinadversesideeffect.com)



# Heightened FQ Concern: *Neuropathy*

**AS** **Alexander Shunnarah**  
PERSONAL INJURY ATTORNEYS  
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## Cipro

**Cipro**, also known as Ciprofloxacin, is used to treat a number of infections which include the following: respiratory tract infections, urinary tract infections, gastroenteritis, bone and joint infections, among others. It is marketed by Bayer A.G. As a result of such adverse reactions, additional warnings, together with "dear doctor letters," and black box labels have been added. The FDA requested warning labels be added identifying peripheral neuropathy (irreversible nerve damage), and heart problems contributing to the severity of these reactions. Ciprofloxacin has generated billions of dollars in revenue. Bayer's gross sales of Cipro were approximately \$1.04 in 1999. A lawsuit was filed in 2003 involving postal workers against Bayer during the Anthrax scare in which the workers suffered serious side effects after being given Cipro. If you or a loved one took Cipro and need more information, **please call Alexander Shunnarah Personal Injury Attorneys today at 800-808-9083.**

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[\[+\]](#)

Car Accidents



Top 10 Car Accident



Drunk Driver



Car Wrecks



Uninsured Motorist



Motorcycle Accidents



Truck Wreck

Nursing Homes

# Heightened FQ Concern: *Neuropathy*

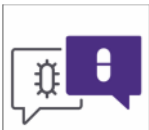
1997-2010

## ■ ADVERSE EVENT REPORTING SYSTEM (AERS) ■

2,500 deaths linked to,  
but not necessarily caused  
by quinolones



45,000 negative side effects



# Heightened FQ Concern: *Neuropathy*



"no 'common thread' of negative evidence that would lead the agency to remove quinolones from the market"

## FDA Black Box Warnings

- 2008: Tendonitis
- 2011: Myasthenia Gravis exacerbation
- 2013: Peripheral Neuropathy



# Heightened FQ Concern: *Neuropathy*



U.S. Department of Health and Human Services



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### Drug Safety and Availability

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## FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

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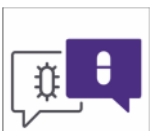
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This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on **May 12, 2016**



## List of Serious Side Effects from Fluoroquinolones for Systemic use

Musculoskeletal and Peripheral Nervous System	Central Nervous System
Tendinitis	Anxiety
Tendon rupture	Depression
Numbness or tingling of extremities	Hallucinations
Muscle weakness	
Muscle pain	
Joint pain	
Joint swelling	
Other Body Systems	
Worsening of myasthenia gravis	
Skin rash	
Sunburn	
Abnormal, rapid or strong heart beat	
Severe diarrhea	

Tendinitis Risk: 2.4 / 10,000

ATR Risk: 1.2 / 10,000

### Tendon Injury Risk Factors

- ✓ Advanced Age
- ✓ Male Gender
- ✓ Low GFR
- ✓ Rheumatologic Dz
- ✓ Corticosteroid use
- ✓ Hyperlipidemia
- ✓ Hyperparathyroidism
- ✓ Physical Activity

<http://www.fda.gov/Drugs>

# Heightened FQ Concern: *Neuropathy*

“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



# Heightened FQ Concern: *Aortic Rupture*

## Drugs

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### Drug Safety and Availability

Drug Alerts and Statements

Medication Guides

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## FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients



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12-20-2018

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>



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.”

Pasternak B BMJ 2018 (N=360,088)

- Retrospective cohort: rupture  $\geq$  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.

Daneman N BMJ Open 2015 (N=657,950)

- Retrospective cohort: rupture  $\geq$  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)



Lee CC JACC 2018 (N=1,213)

- Self-controlled analysis: elderly pts 60 time
- FQ exposure **OR=2.71 (95% CI=1.14-**
- 3-14 days OR=2.41 (95% CI=1.25-4.6
- 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.

# Heightened FQ Concern: *Aortic Rupture*

“Health care professionals should avoid prescribing FQ antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, 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*

## Implications... Threats... Opportunities

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

### 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, gnawing 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

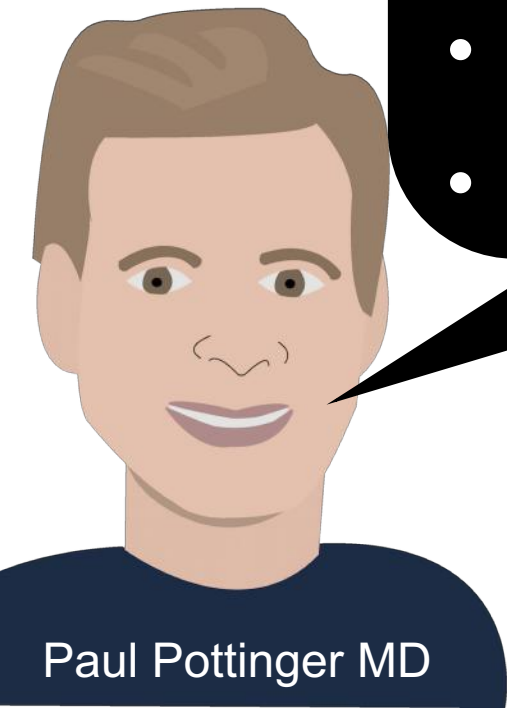
- Contact your health care professional immediately if you experience any serious side effects while you are taking your fluoroquinolone antibiotic.
- Before starting a new fluoroquinolone antibiotic, inform your health care professional if you have previously experienced any serious side effects with 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.



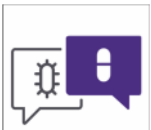
# Fluoroquinolones: *Question*

Do you have a pt  
information sheet on  
FQ toxicity?

- Yes
- No
- Not Sure

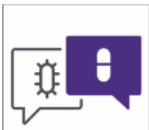


Paul Pottinger MD



# Fluoroquinolones: *UTI Alternatives....*

- Nitrofurantoin (*Macrobid*) 100mg PO BID x 5 d (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



# Fluoroquinolones: *UTI Alternatives....*

- Nitrofurantoin (*Macrobid*)  
5 d (caution in renal impairment)  
*Puget Sound: ~20% Resistance*

- TMP/SMX (*Bactrim*) resistance <20%:  
1 DS PO BID x 3 days

*Modified IDSA  
recommendations  
soon?*

- Ciprofloxacin 500mg PO BID x 1 dose

- TMP/SMX resistance <20%:

- ✓ Cipro 500mg PO QD x 3 days *OR*
- ✓ Cefpodoxime 100mg PO BID x 7 days



# Fluoroquinolones: *Sinusitis Alternatives....*

## 1<sup>st</sup> Line Empiric Abx

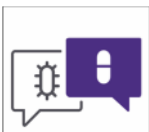
- Amox-Clav 875-2000 mg PO BID x 5-7 Days

## 2<sup>nd</sup> Line Empiric Abx

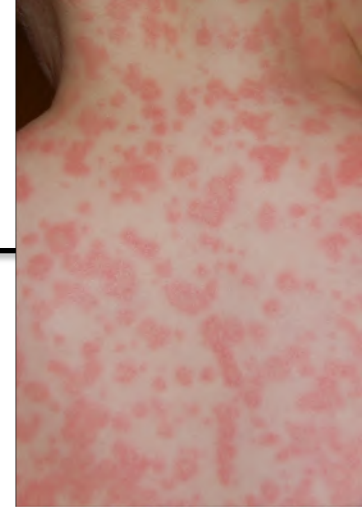
- Doxycycline 100 BID or
  - Levofloxacin 500 QD or
  - Moxifloxacin 400 QD
- } 5-7 Days

## No Longer Recommended

- Azithromycin, TMP/SMX



# Penicillin Allergies

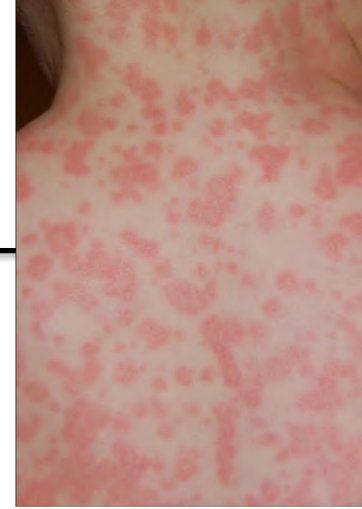
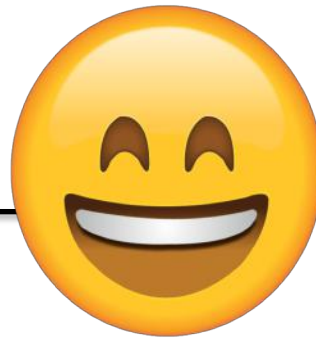


## “A Hot Mess”

“I’m Allergic:” **Please figure this out!**

- 10% of Americans report a “PCN allergy”
- **> 90% of these are bogus! (nausea, yeast infxn....)**
- **50% increase in surgical site infections and adverse reactions** with second-line abx (vanco alone, clinda, FQ)
- **Inferiority** of clinda vs PCN or amox for most dental infections and surgical prophylaxis
- If reaction was not life-threatening, oral amox challenge always safe, and **> 95% have no reaction!**

# Penicillin Allergies

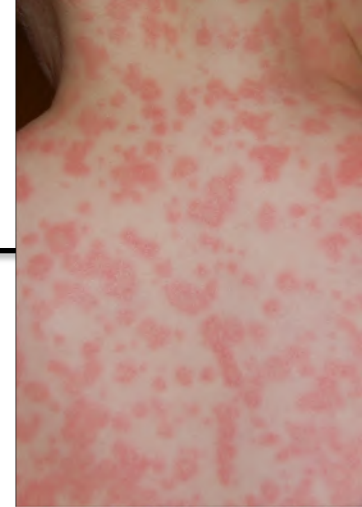
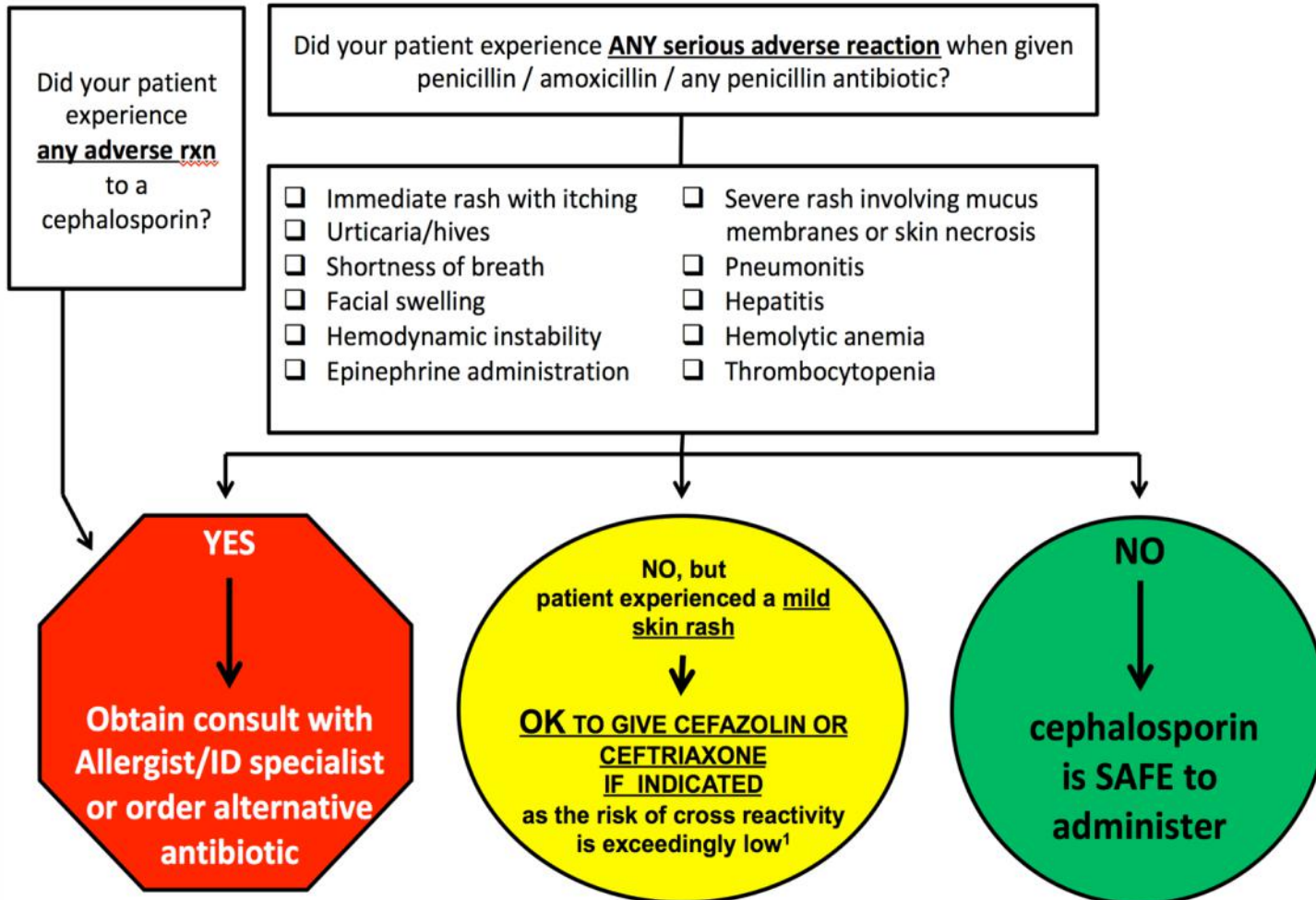


## “History is key”

- **WHAT?** (Airway? Intubation? Itching? “Hives” used differently by many 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!**

# Penicillin Allergies

## ASSESSING PENICILLIN ALLERGY PRE-OP



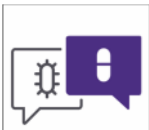
# Fluoroquinolones: *Question*

Do you have an allergy assessment pathway?

- Yes
- No
- Not Sure



Paul Pottinger MD



BEING A  
**DOCTOR**

IS EASY, IT'S LIKE  
**RIDING A BIKE**

EXCEPT THE BIKE IS ON FIRE  
YOU'RE ON FIRE  
EVERYTHING IS ON FIRE  
AND YOU'RE IN HELL

# Conclusions: *Quinolone Toxicity*

- They're great drugs!
- Too bad they can be so TOXIC
- When reaching for FQ, pause and ask "Is this indicated? Is there something safer? Has pt given informed consent?"



Paul Pottinger MD

