[Hyper]sensitivities

CLINID conference
Hunter Ratliff
01/23/2025

Ages, dates, and other identifying information may have been changed
I have no conflict of interest in relation to this presentation

Case #1

Case 1: HPI

A **54 y/o M** with PMH including T2DM (A1c 9.6), psoriasis, congenital foot deformity p/w **fevers**

Case 1: Backstory

A **54 y/o M** with PMH including T2DM (A1c 9.6), psoriasis, congenital foot deformity p/w **fevers**

Admitted 5 weeks ago (- 36d) for MRSA bacteremia

- Bacteremia 2/2 left great toe OM (s/p amputation with + margins; - 33d)
- Cleared cultures on first set of repeats
- Possible healed aortic valve vegetation on TEE
- Has been on daptomycin + cefepime + Flagyl for past 5 weeks (1 more week to go)

Case 1: Backstory

A **54 y/o M** with PMH including T2DM (A1c 9.6), psoriasis, congenital foot deformity, **recent MRSA bacteremia** 2/2 toe OM c/b possible AoV endocarditis (on DAP/FEP/MTZ for past 5 weeks) p/w **fevers**

- Admitted 5 weeks ago (- 36d) for MRSA bacteremia 2/2 toe OM, discharged 4 weeks ago
- Readmitted 2 weeks ago for fevers while on OPAT
    - During his two day readmission, fevers attributed to his newly discovered PICC associated DVT
    - No change in antimicrobials

Case 1: Medical history

A **54 y/o M** with PMH including T2DM (A1c 9.6), psoriasis, congenital foot deformity, **recent MRSA bacteremia** 2/2 toe OM c/b possible AoV endocarditis (on DAP/FEP/MTZ for past 5 weeks), recent fevers from PICC associated DVT p/w **fevers**

- **Allergies:** **Itchy rash** with chills after he got **penicillin** as a teenageer
- **Psoriasis:** Has some baseline rash, managed well with topicals
- **Congenital foot deformity:** Remote history of surgery, but no hardware

Case 1: HPI

A **54 y/o M** with PMH including T2DM (A1c 9.6), psoriasis, congenital foot deformity, **recent MRSA bacteremia** 2/2 toe OM c/b possible AoV endocarditis (on DAP/FEP/MTZ for past 5 weeks), recent fevers from PICC associated DVT p/w **fevers**

- Since most recent discharge (2 weeks ago), has noted **dry cough**
  - Eventually developed to **pleuritic chest pain**
  - No dyspnea
- Four days ago, started **having infusion reactions** shortly after giving cefepime
  - Transient sensation of swelling/**fullness in his bilateral submandibular jaw**/neck with associated **stomach/upper abdominal discomfort**
  - No new/changed rash or pruritus
- Starting yesterday, developed **fevers** (to 101's)
  - Questionable if temporally related to cefepime

Case 1: Social, Exposures, Risk Factors

Geographic & Occupational: The patient lives in Morgantown, West Virginia with his wife. He denies recent travel. No worrisome risk factors for Legionella (has not worked on water tanks, AC, plumbing). States **he works in "IT"**; when asked further he states his employer is "**one of the three letter abbreviations**" and that he **cannot provide any further details about his occupation**.

Substance: They deny alcohol use and he does not use tobacco . They report no recreational drug use

Animal Exposures: The patient denies farm animal exposures, bird/reptile exposures, or other animal exposure (aside from their pet cat).

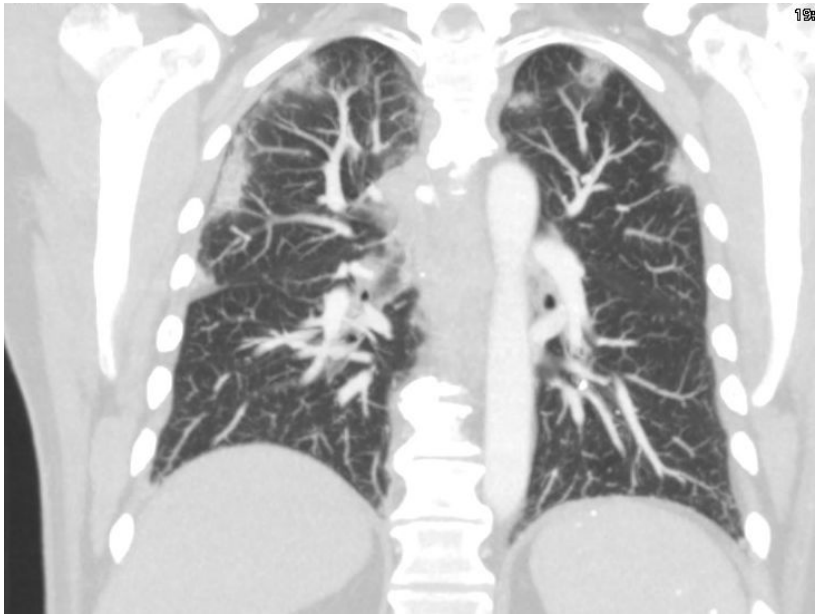
Tattoos & Piercing: They have have not gotten unprofessional piercings or tattoos .

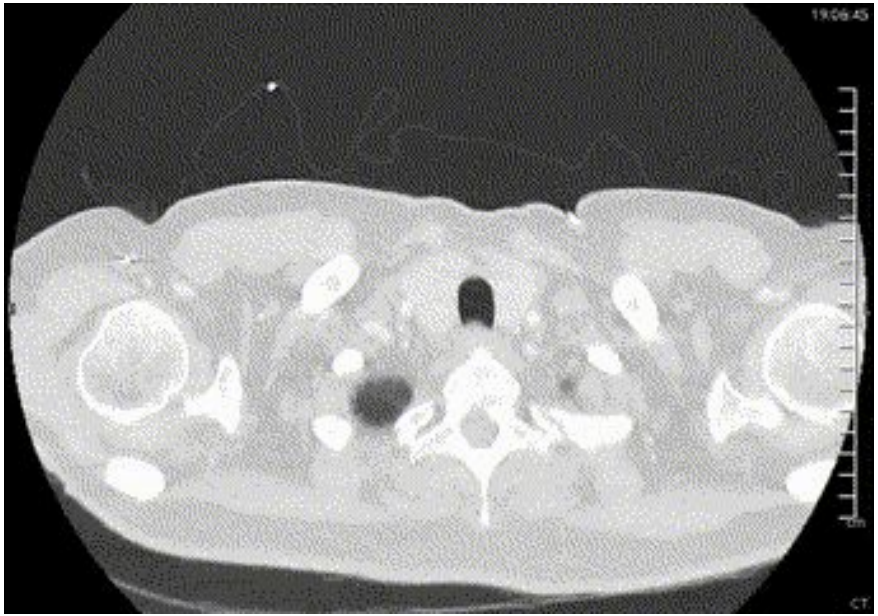
Infectious PMH: They **reports previous intolerances/allergies to antimicrobials** (itchy rash with penicillin in teenage years); They deny history of C. diff infections. He denies known prior exposure to tuberculosis. No known sick contacts, and has not been in public (works remotely for past weeks) much because of frequency of IV antibiotics

Case 1: Exam

Vitals: BP 122/75 | Pulse 97 | 36.9 °C (98.4 °F) | SpO2 93% | BMI 29.71
Gen: alert and oriented, NAD, vitals reviewed
Head/Neck: NCAT; trachea appears midline, no gross LAD
ENT: EOMI grossly, anicteric sclerae; MMM
Resp: normal respiratory effort, symmetric chest rise
CV: RRR; extremities perfused
GI: non-distended; no TTP
Skin: **Rash on BUE>BLE c/w known psoriasis**; no nail changes
Neuro/MSK: moves extremities; **b/l feet look good**
Lines: No pain or erythema at site of PICC line

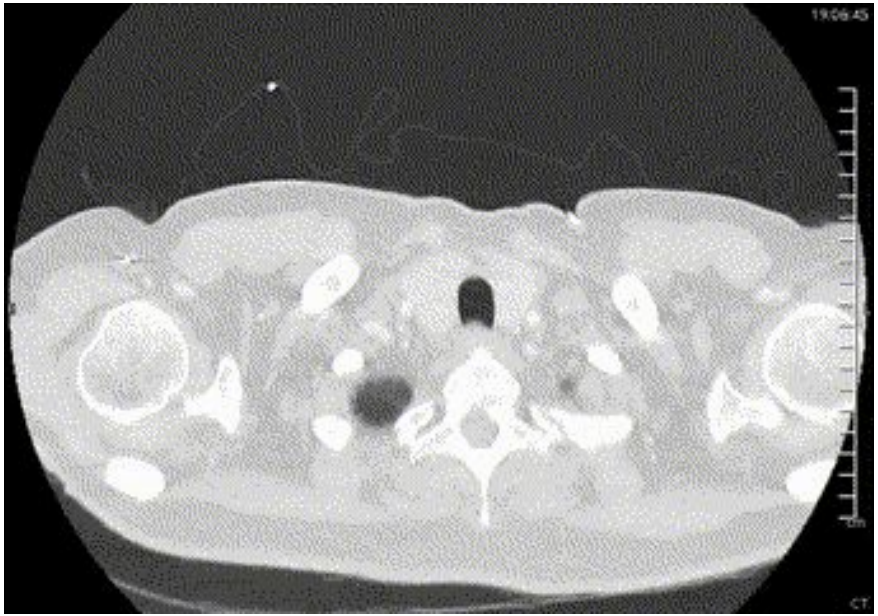
Case 1: Imaging





Case 1: Imaging

1. **Multifocal bilateral groundglass and consolidative opacities, concerning for multifocal pneumonia**. Groundglass nodule in the posterior left upper lobe measuring 8.9 x 5.6 mm. Multiple additional groundglass appearing nodules within the peripheral areas of the lungs.
2. Moderate-sized hiatal hernia.
3. Cholelithiasis without evidence for cholecystitis.
4. Prominent right thyroid nodule measuring up to 1.5 cm. Recommend follow-up ultrasound on nonemergent basis.



Case 1: Labs

	Admission	Discharge (2 weeks ago)
WBC	**0.6**	6.6
Hgb	13.7	14.9
PLTs	323	262
Neutrophils	**<0.10** (4%)	3.43 (52%)
Lymphocytes	**0.50** (83%) (15% reactive)	1.48 (22%)
Monocytes	**<0.10** (13%)	0.91 (14%)
Eosinophils	<0.10 (0%)	**0.72** (11%)
Basophils	<0.10 (0%)	<0.10 (1%)

CRP: 27 (down from 90)

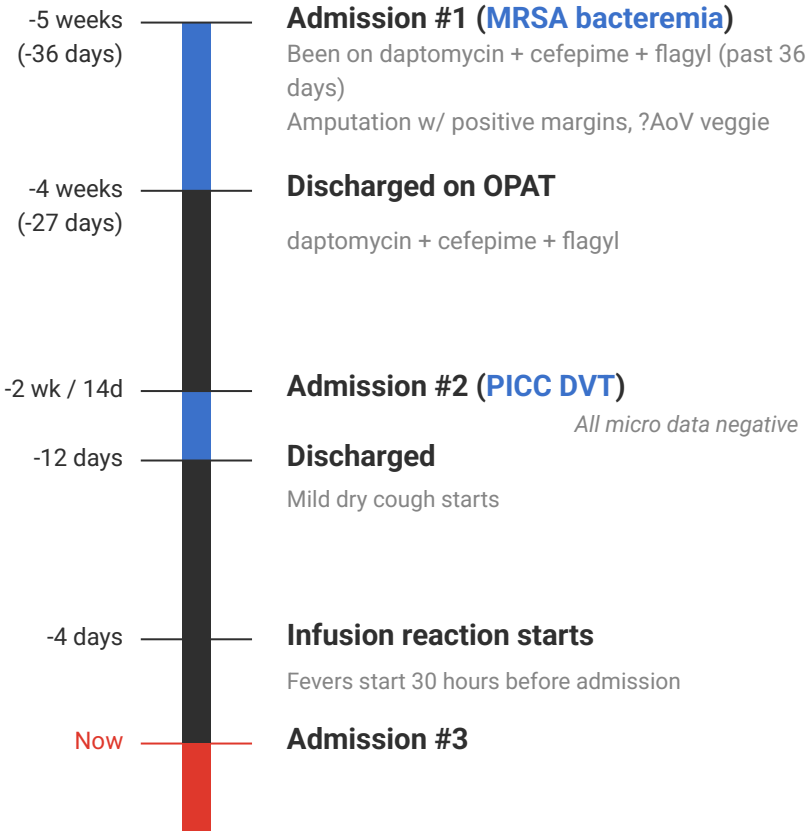
Chem7: Normal

LFTs: Not checked

Case 1: Summary

A **54 y/o M** w/ T2DM (A1c 9.6), psoriasis, congenital foot deformity, **recent MRSA bacteremia** 2/2 toe OM c/b possible AoV endocarditis, recent fevers from PICC associated DVT

- 2 weeks dry cough, peripheral opacities on CT
- 4 days of infusion reactions, seemingly with cefepime
- Two episodes of fevers while on antibiotics
- Leukopenia, recent eosinophilia



Case 1: Summary

A **54 y/o M** w/ T2DM (A1c 9.6), psoriasis, congenital foot deformity, **recent MRSA bacteremia** 2/2 toe OM c/b possible AoV endocarditis, recent fevers from PICC associated DVT

- 2 weeks dry cough, peripheral opacities on CT
- 4 days of infusion reactions, seemingly with cefepime
- Two episodes of fevers while on antibiotics
- Leukopenia, recent eosinophilia

1. Medicine pages at 8pm asking if he needs admission. Does he?
2. DDx for the labs?
3. Are his fevers infectious or non-infectious?
4. Empiric treatment for neutropenic fever?

	Admission	**Discharge** (2 weeks ago)
WBC	**0.6**	6.6
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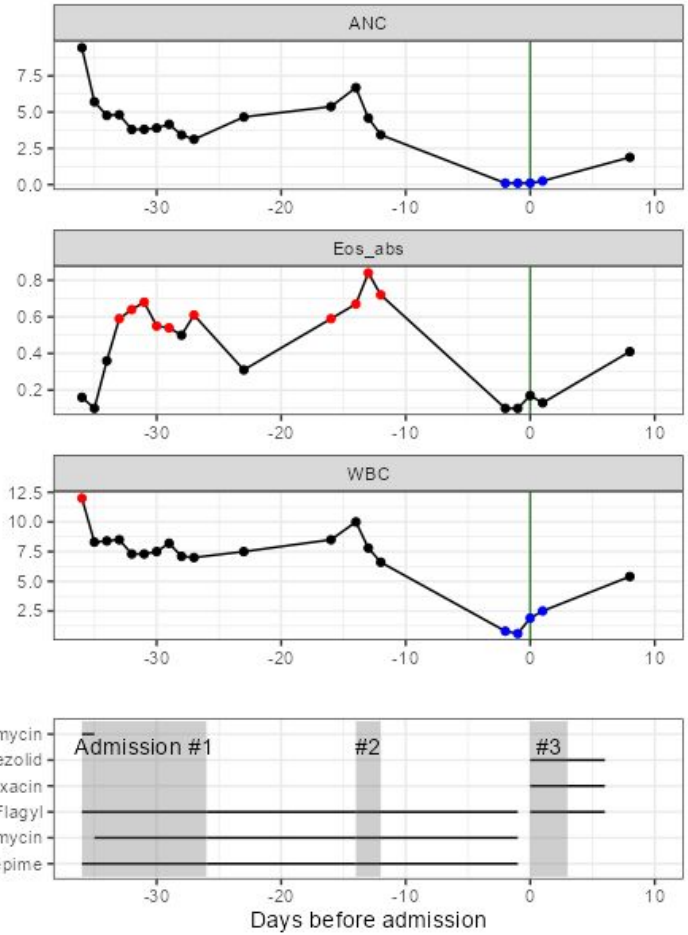
Case 1: Hospital course

- Blood cultures negative
- Presumed neutropenia from cefepime
- Fevers stopped with stopping antibiotics
- Given neutropenic fever & CT findings:
  - Switched to Levaquin & Zyvox
  - Continued flagyl for treatment of OM
- Counts recovered with stopping cefepime
- Doing well off antibiotics at clinic visit



Case #2

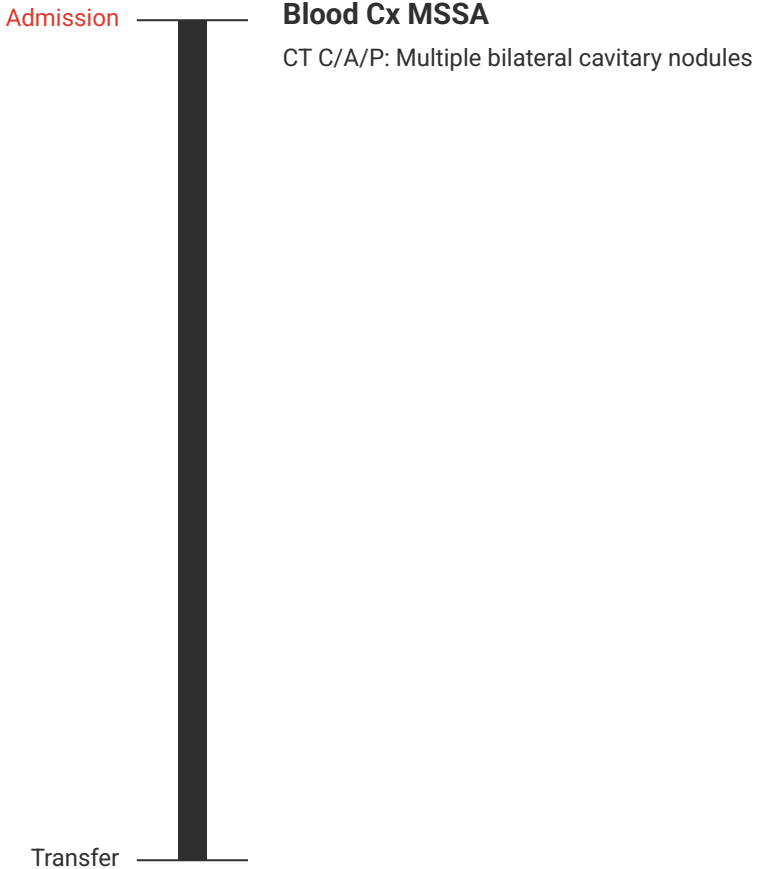
Case 2: HPI

A **37 y/o M** with PMH including PWID (sober for 2 months) was admitted to OSH 10 days ago for **MSSA tricuspid valve endocarditis** and was transferred for advanced GI evaluation

Case 2: OSH (Day 1)

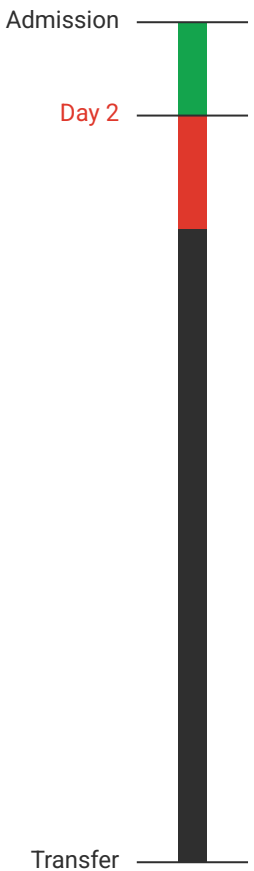
A **37 y/o M** with PMH including PWID (sober for 2 months) was admitted to OSH 10 days ago for **MSSA tricuspid valve endocarditis**

- Presented with fevers, dyspnea, and back pain
- Blood cultures positive (would be MSSA)
- **CT C/A/P**: Multiple bilateral cavitary nodules



Case 2: OSH (Day 2 & 3)

- TTE: **10-15mm tricuspid valve** vegetation
  - No formal bubble study
- ID consulted
  - Switched from vanc & ceftriaxone to **Ancef**
  - **HIV & HCV screen** negative



Blood Cx MSSA

CT C/A/P: Multiple bilateral cavitary nodules

TTE: 1.3 cm tricuspid veggie

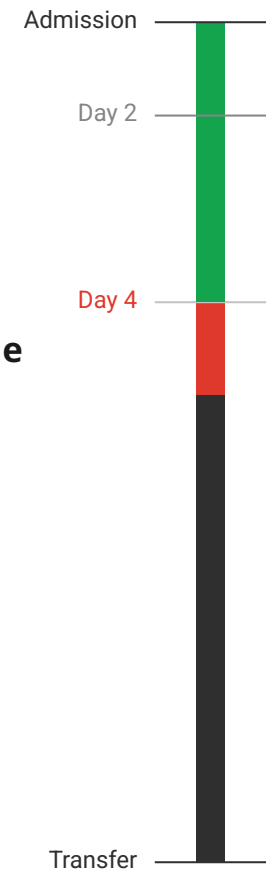
MRI L-spine normal

Started Ancef

HIV & HCV negative

Case 2: OSH (Day 4)

- Blood cultures clear by day 4
- Not documented in the EMR, but this is **when the patient first noticed a new rash**



Blood Cx MSSA

CT C/A/P: Multiple bilateral cavitary nodules

TTE: 1.3 cm tricuspid veggie

MRI L-spine normal

Started Ancef

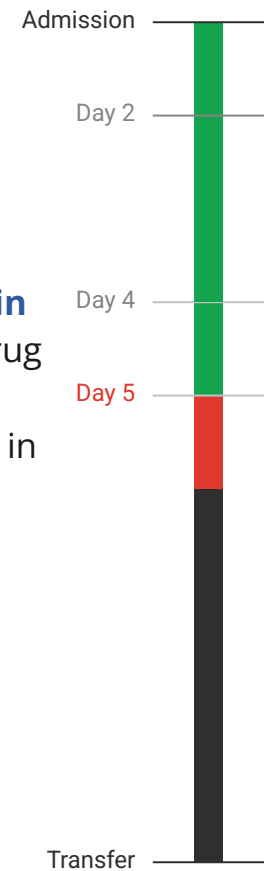
HIV & HCV negative

Developed rash (per patient)

Blood cultures cleared

Case 2: OSH (Day 5)

- "Nurses found a **cigarette/pipe looking object in his bed with brown residue**. I did do a urine drug screen and it is still positive for fentanyl. Should be negative by now. Usually is out of the system in 24-72 hours… Patient has been *acting 'funny'* per nursing"



Blood Cx MSSA

CT C/A/P: Multiple bilateral cavitary nodules

TTE: 1.3 cm tricuspid veggie

MRI L-spine normal

Started Ancef

HIV & HCV negative

Developed rash (per patient)

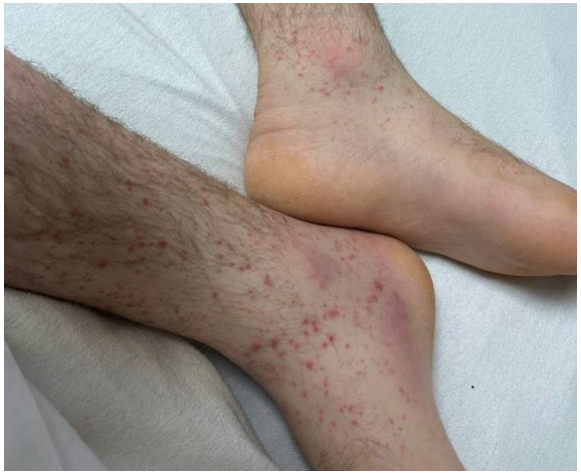
Blood cultures cleared

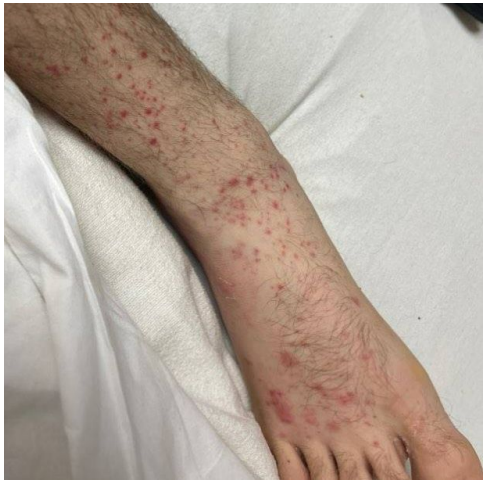
Nursing found a pipe with brown residue

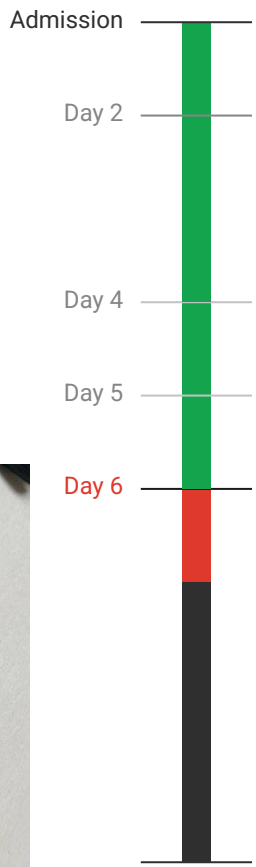
UDS w/ fentanyl (should be negative by now)

Case 2: OSH (Day 6)

- Now there are finally pictures of the rash







Blood Cx MSSA

CT C/A/P: Multiple bilateral cavitary nodules

TTE: 1.3 cm tricuspid veggie

MRI L-spine normal

Started Ancef

HIV & HCV negative

Developed rash (per patient)

Blood cultures cleared

Nursing found a pipe with brown residue

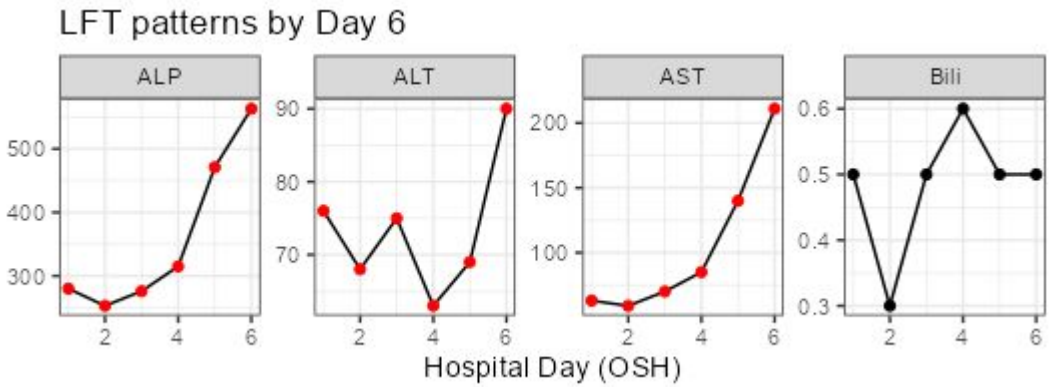
UDS w/ fentanyl (should be negative by now)

Ancef changed to vanco (LFT increase)

First pictures of the rash

Case 2: OSH (Day 6)

- Some **LFT elevation**, so changed from Ancef to **vancomycin**



Admission — **Blood Cx MSSA**

CT C/A/P: Multiple bilateral cavitary nodules

Day 2 — **TTE: 1.3 cm tricuspid veggie**

MRI L-spine normal

Started Ancef

HIV & HCV negative

Day 4 — **Developed rash (per patient)**

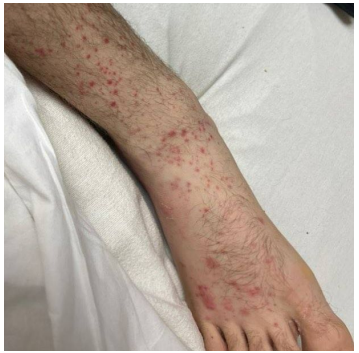
Blood cultures cleared

Day 5 — **Nursing found a pipe with brown residue**

UDS w/ fentanyl (should be negative by now)

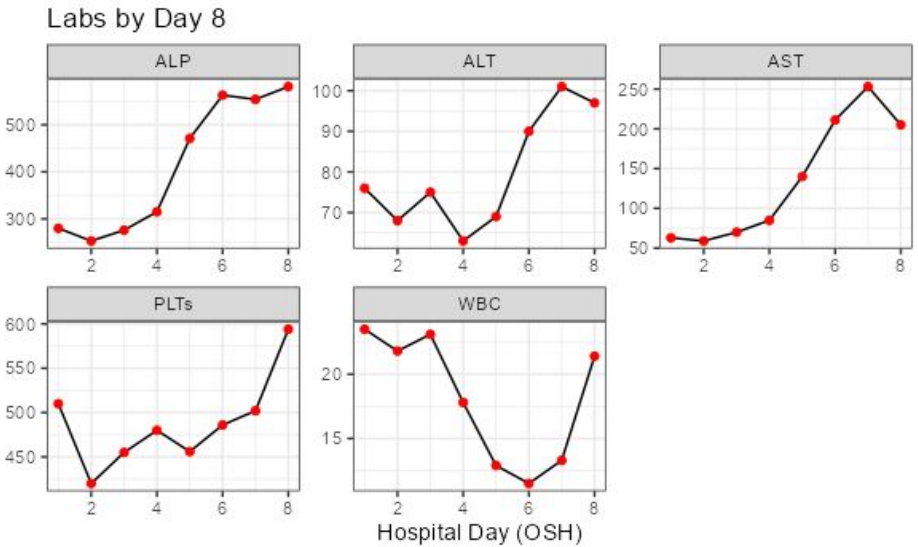
Day 6 — **Ancef changed to vanco (LFT increase)**

First pictures of the rash



Case 2: OSH (Day 8)

- Develops worsening **leukocytosis** (back **in 20s**)
- Ongoing LFT abnormalities (still cholestatic)



Admission
Blood Cx MSSA
CT C/A/P: Multiple bilateral cavitary nodules

Day 2
TTE: 1.3 cm tricuspid veggie
MRI L-spine normal
Started Ancef
HIV & HCV negative

Day 4
Developed rash (per patient)
Blood cultures cleared

Day 5
Nursing found a pipe with brown residue
UDS w/ fentanyl (should be negative by now)

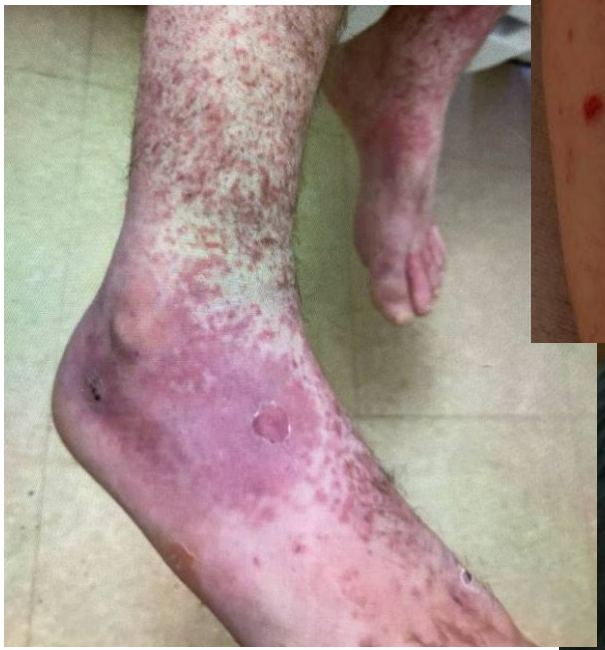
Day 6
Ancef changed to vanco (LFT increase)
First pictures of the rash

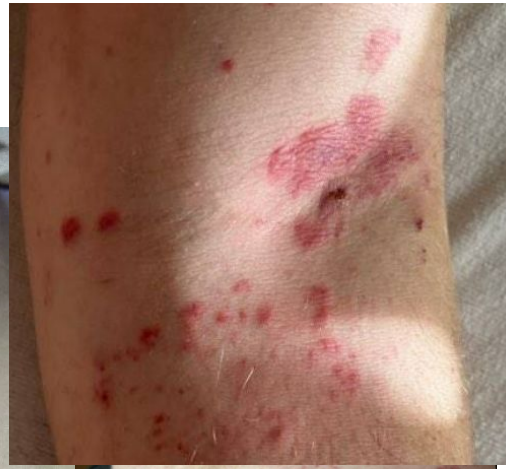
Day 8
WBC begin to rise, LFTs still high
Second pictures of the rash

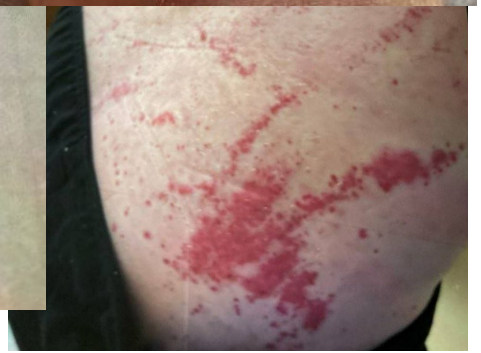
Transfer

Case 2: OSH (Day 8)

Top: L arm; bottom: back







Admission — **Blood Cx MSSA**
CT C/A/P: Multiple bilateral cavitary nodules

Day 2 — **TTE: 1.3 cm tricuspid veggie**
MRI L-spine normal
Started Ancef
HIV & HCV negative

Day 4 — **Developed rash (per patient)**
Blood cultures cleared

Day 5 — **Nursing found a pipe with brown residue**
UDS w/ fentanyl (should be negative by now)

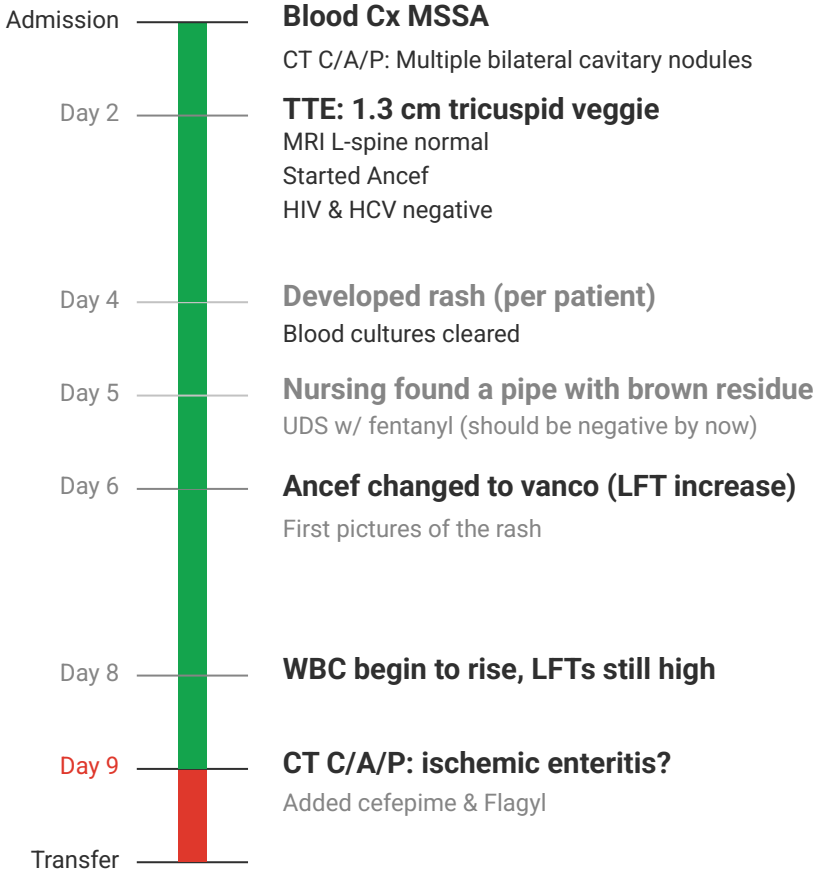
Day 6 — **Ancef changed to vanco (LFT increase)**
First pictures of the rash

Day 8 — **WBC begin to rise, LFTs still high**
Second pictures of the rash

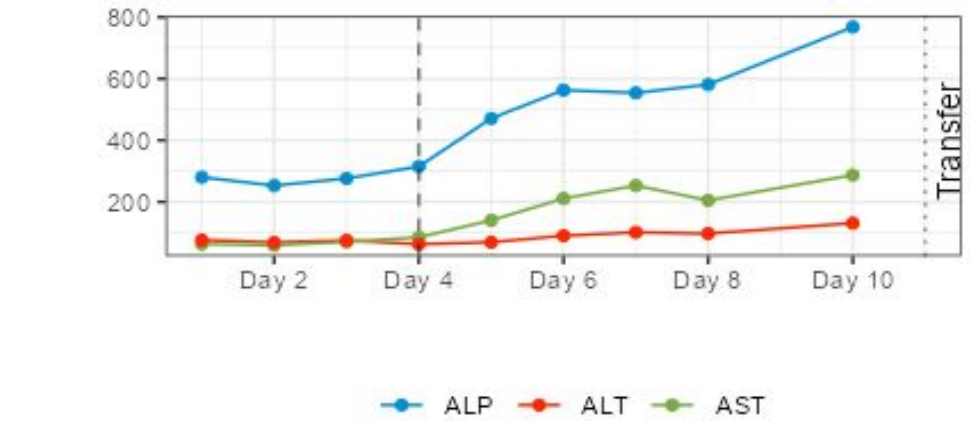
Transfer

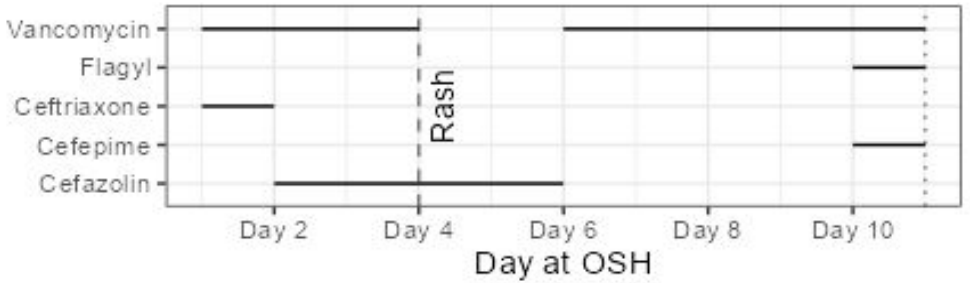
Case 2: OSH (Day 9 & 10)

- CT C/A/P: severe mural thickening/edema involving the crossing duodenum and proximal jejunum c/w **infectious vs ischemic enteritis**
- Surgery recommended transfer for advanced GI evaluation (& in case he needs high risk surgery)
- Added **cefepime & flagyl**



Case 2: Outside hospital course





Micro (OSH)

- Initial & repeat BCx: MSSA
  - Cleared by day 4
- HIV & HCV screen negative
  - HBV non-immune

Imaging

- CT C/A/P (Day 0): Multiple bilateral cavitary nodules
- MRI L-spine (Day 1): Normal
- TTE (Day 1): **1.3 cm tricuspid veggie**
- CT C/A/P (HD #9): severe mural thickening/edema involving the crossing duodenum and proximal jejunum c/w **infectious vs ischemic enteritis**

Case 2: HPI & Social History

Geographic & Occupational: The patient lives in Parkersburg, West Virginia w/ his two teenage children. He denies recent travel. They are not working presently.

Substance: They deny alcohol use and he is a **current 1/2 ppd smoker**. They report prior IVDU with opiates and meth, but have **not used for the past 2 months** and is presently on methadone. **Still smokes weed**. Denies shared needles

Animal Exposures: The patient denies farm animal exposures or other animal exposure (aside from their pet cat, dogs, and **snake**).

Sexual: Not sexually active

Infectious PMH: They deny previous intolerances/allergies to antimicrobials; He denies known prior exposure to tuberculosis.

Case 2: Labs

ALBUMIN 3.5 - 5.0 g/dL	1.8 ⌄	1.7 ⌄	1.7 ⌄
ALKALINE PHOSPHATASE 45 - 115 U/L	961 ^	837 ^	768 ^
ALT (SGPT) <43 U/L	334 ^	236 ^ R	131 ^ R
AST (SGOT) 11 - 34 U/L	933 ^	625 ^ R	287 ^ R
Comment: Hemolysis can alter results at this level (slight).			
BILIRUBIN TOTAL 0.3 - 1.3 mg/dL	0.8	1.0 CM	0.7 CM

	Admission	Day 3
AMPHETAMINE, URINE	Positive !	Negative
BARBITURATE, URINE	Negative	Negative
BENZODIAZEPINE,URINE	Negative	Negative
BUPRENORPHINE, URINE QL	Negative	Negative
CANNABINOID (THC), URINE	Positive !	Positive !
COCAINE METAB. URINE	Negative	Negative
METHADONE, URINE	Negative	Positive !
URINE OPIATE, LOW CUTOFF	Negative	Positive !
OXYCODONE QUAL, URINE	Negative	Positive !
ECSTASY/MDMA QUAL, URINE	Negative	Negative
FENTANYL, RANDOM URINE	Positive !	Positive !

WBC	10.8
Hgb	**9.4**
PLTs	**631**
Neutrophils	**7.83** (73%)
Lymphocytes	1.91 (18%)
Monocytes	0.65 (6%)
Eosinophils	0.19 (1.8%)
Basophils	<0.10 (0.4%)

HEPATITIS A IGM AB	Negative		
HEPATITIS B SURFACE AG		Negative	
HEPATITIS B CORE AB, IGM	Negative		
HEPATITIS C ANTIBODY	Negative		
HIV SCREEN, COMBINED ANTIGEN & ANTIBODY			Negative
HBV QUANTITATIVE PCR			

Case 2: Consultants

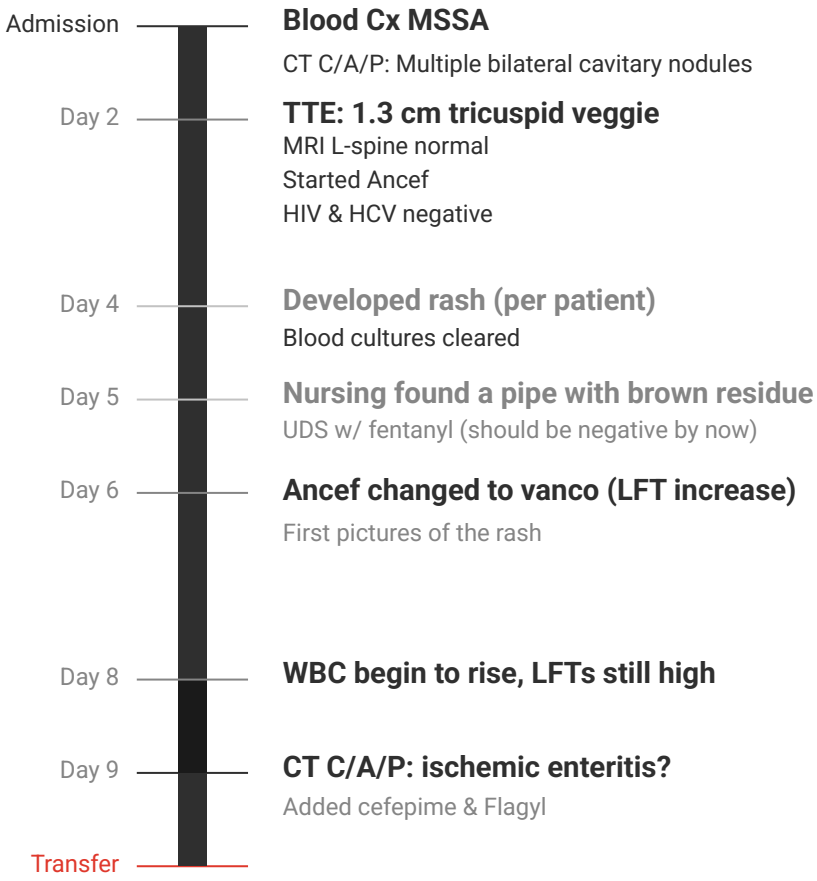
Advanced GI's opinion

- Patient with what appears to be ischemic enteritis based on imaging (CTAP w on 12/6 compared to CT abd w/wo 12/15) with interval worsening in imaging. Abdominal pain, nausea, and vomiting ongoing for 4-5 days with interval improvement since 12/16 and tolerated cheese steak sandwich 12/16 in evening.
- Gen surg following recommending endoscopic evaluation.
- The diagnosis appears to be septic emboli causing ischemic enteritis to celiac trunk (no evaluation for PFO on echo). He was previously symptomatic but is now asymptomatic, asking for diet. Endoscopic evaluation can delineate extent and severity of disease but given clinical exam, unlikely to change overall management. **Would recommend full liquid diet x 48 hours then advance diet as tolerated**. Can repeat
- Elevated liver enzymes, unclear chronicity, from at least 12/6/24. Hepatocellular injury primarily with elevated ALP as well, TB is normal. Suspect possible DILI from IV cephalosporin use vs acute viral illness. Follow-up acute hepatitis serologies. Recommend changing IV cephalosporin to alternative antibiotic if possible (Cephalosporins, Parenteral - LiverTox - NCBI Bookshelf).
- Please call GI fellow on call if patient has an acute GI bleed or develops hemodynamic instability.

Case 2: Summary

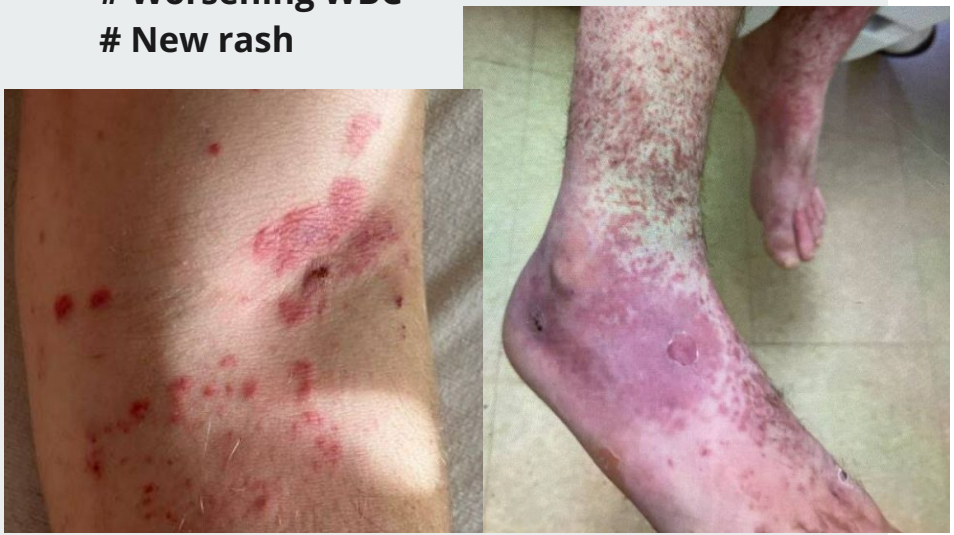
A **37 y/o M** with PMH including PWID (**sober for 2 months**) was admitted to OSH 10 days ago for **MSSA tricuspid valve endocarditis**.

 # MSSA bacteremia
 # Tricuspid valve endocarditis
 # Elevated LFTs
 # Worsening WBC
 # New rash
 # Ischemic vs infectious enteritis

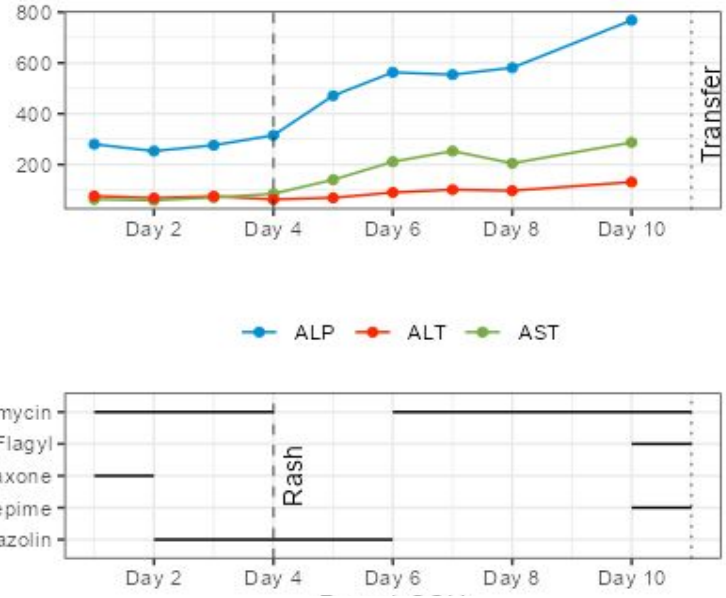


Case 2: Summary

 # MSSA bacteremia
 # Tricuspid valve endocarditis
 # Ischemic vs infectious enteritis
 # Elevated LFTs
 # Worsening WBC
 # New rash



1. Is there a unifying diagnosis that ties in:
   a. LFTs
   b. Rash
   c. CT findings
2. Additional workup?
3. What would you do about the antibiotics?



The red flags

Substance: They deny alcohol use and he is a current 1/2 ppd smoker. They report prior IVDU with opiates and meth, but have **not used for the past 2 months** and is **presently on methadone**. Still smokes weed. Denies shared needles

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BUPRENORPHINE, URINE QL	Negative	Negative
CANNABINOID (THC), URINE	**Positive** !	**Positive** !
COCAINE METAB. URINE	Negative	Negative
METHADONE, URINE	Negative	**Positive** !
URINE OPIATE, LOW CUTOFF	Negative	**Positive** !
OXYCODONE QUAL, URINE	Negative	**Positive** !
ECSTASY/MDMA QUAL, URINE	Negative	Negative
FENTANYL, RANDOM URINE	**Positive** !	**Positive** !

The red flags

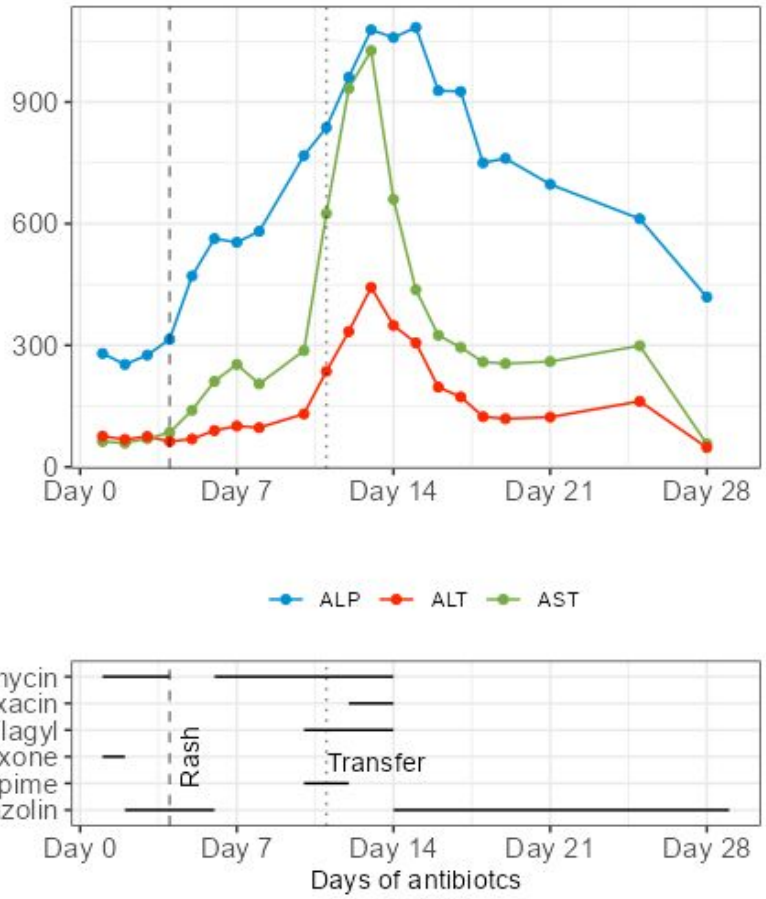
		Other hospital		
HEPATITIS A IGM AB	Negative	Negative		
HEPATITIS B SURFACE AG	Negative		Negative	
HEPATITIS B CORE AB, IGM	Negative	Negative		
HEPATITIS C ANTIBODY	Negative	Negative		
HIV SCREEN, COMBINED ANTIGEN & ANTIBODY	Negative			Negative
HBV QUANTITATIVE PCR	Target Not Detected			

The red flags

		Other hospital			Ruby	
HCV RNA BY PCR, QUANTITATIVE	Target Not Detected IU/ML				7,100,000 ▲	
HCV LOG 10	0.0 LOG10				6.85 ▲	
HEPATITIS A IGM AB	Negative	Negative				
HEPATITIS B SURFACE AG	Negative		Negative			
HEPATITIS B CORE AB, IGM	Negative	Negative				
HEPATITIS C ANTIBODY	Negative	Negative				
HIV SCREEN, COMBINED ANTIGEN & ANTIBODY	Negative			Negative		
HBV QUANTITATIVE PCR	Target Not Detected					Target Not Detected

Case 2: Hospital course

- We started **Levaquin & Flagyl** for intraabdominal coverage
- Diagnosed with **acute HCV**, **switched back to Ancef** without issue
- TEE did not show left sided disease
    - Still don't know about a PFO



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- Diagnosed with **acute HCV**, **switched back to Ancef** without issue
- TEE did not show left sided disease
  - Still don't know about a PFO

- Dermatology saw patient, suspected **early leukocytoclastic vasculitis**
  - Consideration given to **IgA vasculitis** & **cryoglobulinemic vasculitis**
- Biopsy: Superficial perivascular neutrophil-rich dermatitis
  - Immunofluorescence was negative for IgA vasculitis
- Cryoglobulins: negative

Since vasculitis workup was negative (*LCV is a small vessel vasculitis*), enteritis was presumed emboli to the SMA

Discussion

Links to articles discussed here

Side effects of beta-lactams

- Identify select **side effects of beta-lactams**
  - **Leukopenia**
  - **Eosinophilia**
  - **Liver injury**
- Define **acute HCV** infection and recognize the appropriate **workup**
- Explore the **differential diagnosis for vasculitis** in the second case
  - Cryoglobulins
  - Antibiotic induced
  - Infectious

Antibiotic neutropenia: Lam (2023) [1.1]

- Seven year review from Canada
- 2513 cases, 90% had 4-6 wk DOT

Antibiotic induced neutropenia developed in **2.2% of patients**

➔ Other estimates have rates as high as **34%**

- ❖ Cefazolin
- ❖ Ceftazidime
- ❖ Ceftriaxone
- ❖ Rifampin
- ❖ Vancomycin
- ❖ Ampicillin
- ❖ Cloxacillin
- ❖ Penicillin G
- ❖ Zosyn
- ❖ Ertapenem

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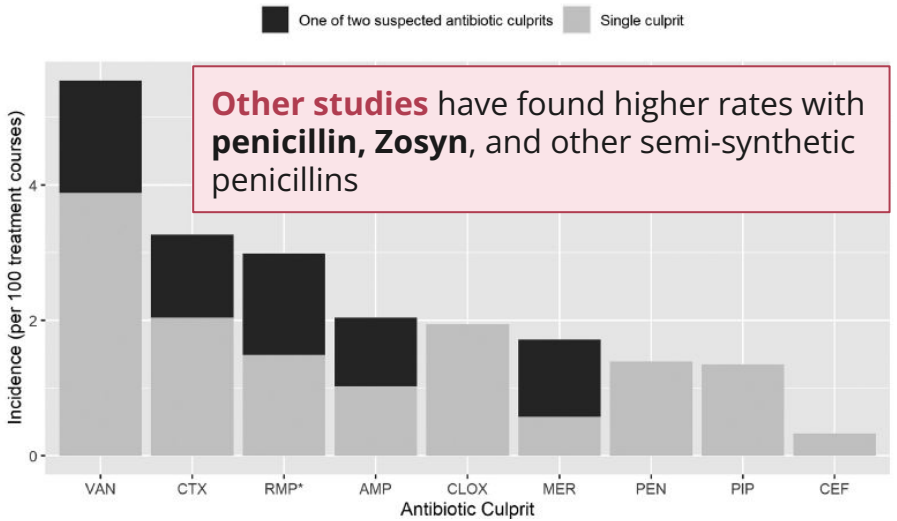
❖ Cefazolin	❖ Ampicillin
❖ Ceftazidime	❖ **Cloxacillin** (1.9%)
❖ **Ceftriaxone** (2.0%)	❖ Penicillin G
❖ Rifampin	❖ Zosyn
❖ **Vancomycin** (3.9%)	❖ Ertapenem



Other studies have found higher rates with **penicillin, Zosyn**, and other semi-synthetic penicillins

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Median **days to neutropenia 25** (IQR 19 to 30)

➔ Similar to other studies

➔ Only **one in four** had any symptoms

IMPRESSION

[redacted] male with a history including poorly controlled diabetes (A1c 9.6), psoriasis, congenital foot deformity, PICC associated DVT, MRSA bacteremia & left great toe OM [redacted] possible AoV vegetation (TEE [redacted]) who was admitted on [redacted] with leukopenia and fevers at home. Patient is well known to the ID service, with multiple admissions as outlined below. He has been on dapto, cefepime, and flagyl since [redacted], and had a precipitous drop in his WBC count between days 23 and 33 of therapy. He also developed an infusion reactions with cefepime (facial swelling and abd pain) followed by fevers at home (early AM hours on [redacted] while still on OPAT). After he was discovered to be leukopenic, OPAT instructed him to hold the antibiotics and present to ED if he had any fevers. He fevered again around noon on [redacted] (got cefepime 4-5 hours before), so presented to ED on [redacted] for further care. CT chest showed b/l peripheral GGOs and respiratory BioFire was negative. He has remained afebrile off antibiotics thus far.

 # Leukopenia, neutropenia
 # Fevers at home
 # Cefepime infusion reaction

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- ❖ Cefazolin
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- ❖ **Ceftriaxone** (2.0%)
- ❖ Rifampin
- ❖ **Vancomycin** (3.9%)
- ❖ Ampicillin
- ❖ **Cloxacillin** (1.9%)
- ❖ Penicillin G
- ❖ Zosyn
- ❖ Ertapenem

In 16% of cases, the culprit beta-lactam antibiotic was **changed to another beta-lactam** agent **containing a structurally different side chain**

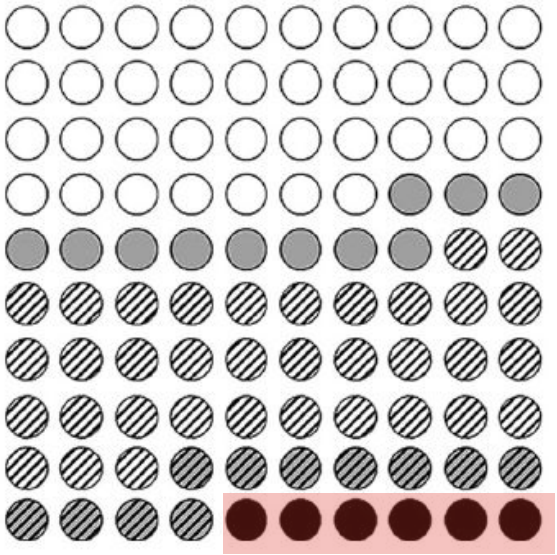
- **Counts recovered in 100%** of cases
- Applied similar principles to IgE-mediated hypersensitivity

Beta-Lactam OPAT: Zukauckas (2022) [1.2]

- 18 month review from Utah, n=264
- Only focused on beta-lactams (so had patients on cefepime, unlike Lam)
- **67% were on cephalosporins**

Beta-Lactam OPAT: Zukauckas (2022) [1.2]

- 18 month review from Utah, n=264
- Unlike Lam (2023), had patients with cefepime



52% of patients had abnormal labs

- **35%** had no change in OPAT
- **11%** had a change, but not due to labs
- **Only 5.7% had a change in therapy** due to labs

Normal labs, no change in therapy (N = 97)

Normal labs, change in therapy (N = 28)

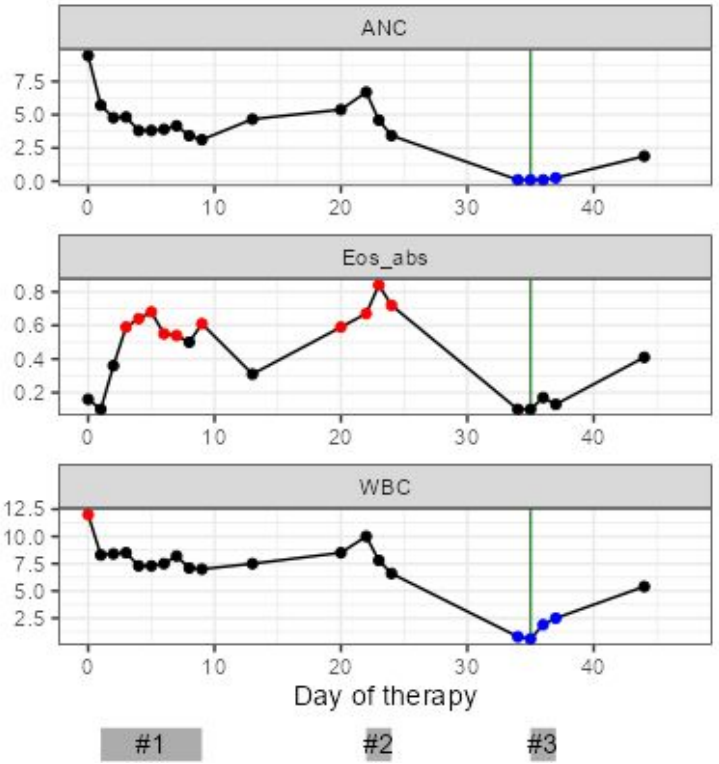
Abnormal labs, no change in therapy (N = 93)

Abnormal labs, change in therapy not due to labs (N = 29)

Change in therapy due to labs (N = 17)

Eosinophilia [1.3]

- Estimates vary, but development of **eosinophilia is common**. In one study [1.3]:
  - Incidence: **One in four patients**
  - Median onset: **15 days** (IQR 8 to 22)
  - **Peak: 726/mL** (IQR 595 to 990)



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- Estimates vary, but development of **eosinophilia is common**. In one study [1.3]:
  - Incidence: **One in four patients** (210/827)
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  - **Peak: 726/mL** (IQR 595 to 990)

	All patients (n = 824)	Multivariate HR* (95% CI)	Multivariate *P* value*
Age, median (IQR)	60 (48-71)	1.02 (1.00-1.03)	.0007
Male sex, no. (%)	494 (60)	0.95 (0.72-1.26)	>.50
Antibiotic,† no. (%)			
Vancomycin	314 (38)	1.66 (1.22-2.26)	.001
Penicillins	207 (25)	1.45 (1.02-2.06)	.03
Metronidazole	123 (15)	0.46 (0.27-0.77)	.003
Rifampin	107 (13)	1.47 (1.03-2.11)	.03
Linezolid	31 (4)	2.09 (1.07-4.06)	.03
Cephalosporins‡	347 (42)		
Flouroquinolones‡	110 (13)		
Carbapenems‡	58 (7)		
Daptomycin	54 (7)		

Table 2 [1.3] Predictors of eosinophilia. Multivariate was only done if univariate model had p < .50

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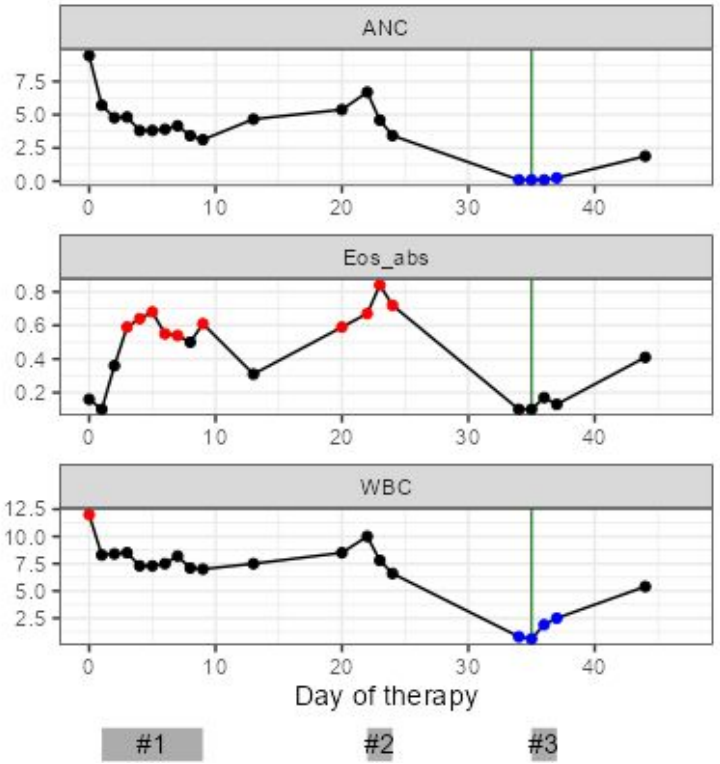
- **Most are asymptomatic**, but some cases are associated with **hypersensitivity reaction** (HSR)
  - **21%** [1.4] **to 30%** [1.3] of cases a/w HSR
  - Cases with HSR had **earlier onset of eosinophilia** (11 vs 17 days)



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- Peripheral eosinophilia **increases rates of rash** (**x4**) and **renal injury** (**x2**) compared to those without eosinophilia

	HR (95% CI)	**P-value**
Rash	4.16 (2.54-6.83)	<0.0001
Renal injury	2.13 (1.36-3.33)	0.0009
Liver injury	1.75 (0.92-3.33)	0.09
Any injury	2.65 (1.94-3.62)	<0.0001

Table 3 [1.3] Eosinophilia as predictor of subsequent HSR

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Table 3 [1.3] Eosinophilia as predictor of subsequent HSR

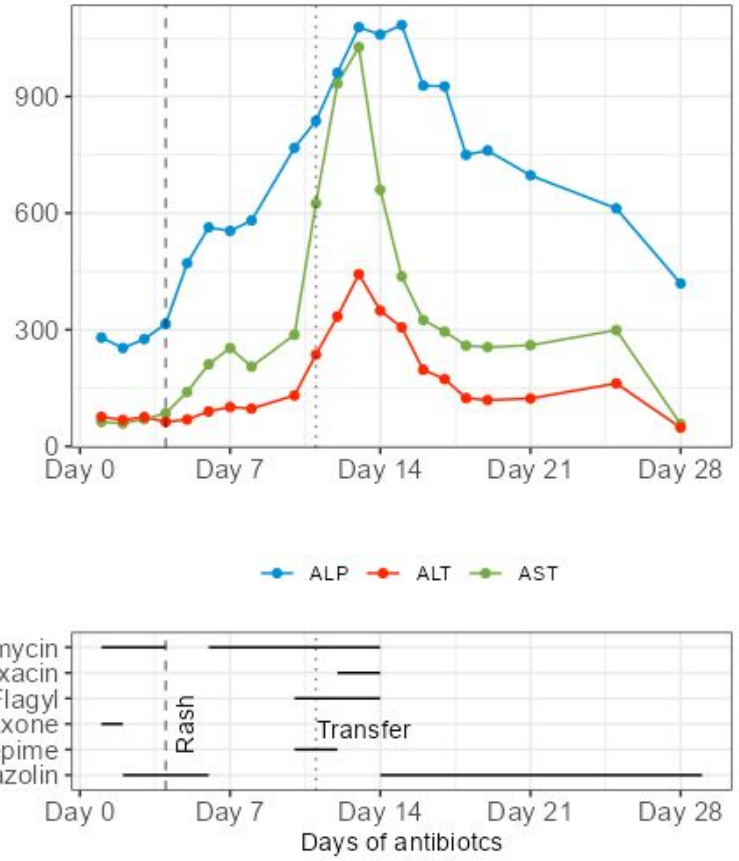
Don't forget the base rate
70% of patients with eosinophilia do fine; eosinophilia should only heighten awareness for possible HSR

Cephalosporin induced DILI [3.1]

Well described, and fairly common as a class

- Up to 11% in frequency
- Most cases are very mild
  - Almost all are asymptomatic
  - **<1%** of cases have **AST/ALT over x5 ULN**
- Likely due to hypersensitivity
- Abrupt onset, **1-4 weeks** after first dose

Case #2 (acute HCV)



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Cefazolin

- In the top 10-15 causes of drug induced jaundice
- Often **cholestatic pattern**, but can be hepatocellular pattern
- Commonly accompanied by **fever, rash &/or eosinophilia**

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- Commonly accompanied by **fever, rash &/or eosinophilia**

Ceftriaxone

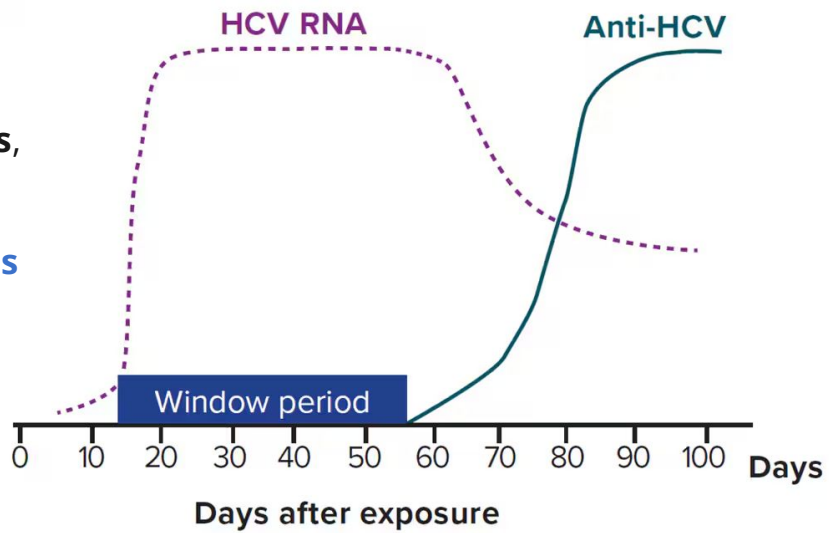
- 3% - 46% frequency
- Most common is "**pseudolithiasis**"
  - Gallstones made of ceftriaxone
  - Only 5% have symptoms
  - Resolve with stopping the drug
- Can also have the **immunoallergic form of cholestatic hepatitis** (seen as a class)

Acute HCV

- Identify select **side effects of beta-lactams**
  - Leukopenia
  - Eosinophilia
  - Liver injury
- Define **acute HCV** infection and recognize the appropriate **workup**
- Explore the **differential diagnosis for vasculitis** in the second case
  - Cryoglobulins
  - Antibiotic induced
  - Infectious

Acute HCV: Timing [2.1, 3.2]

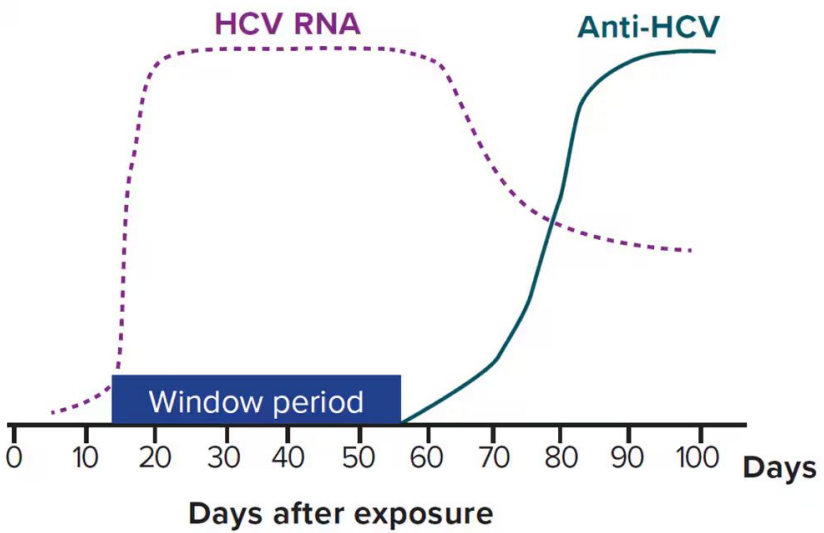
- By convention, “acute HCV” refers to the **first 6 months** of HCV infections
- **HCV RNA** becomes detectable in **days to 8 weeks**, most often **by 2 weeks**
- **HCV antibodies** seroconvert between **2-6 months**



LFT abnormalities will often be present **before the antibody** is present

Acute HCV: When to get a PCR [2.1, 3.2]

- Guidelines suggest obtaining HCV Ab **& PCR** if **exposure is <6 months** & **signs/labs suggestive of acute hepatitis**
  - i.e. acute, moderate transaminitis (>5x ULN)
- Most "*acute hepatitis panels*" (Quest, Labcorp, ARUP) **don't include standalone HCV PCR**, only antibody with reflex to PCR



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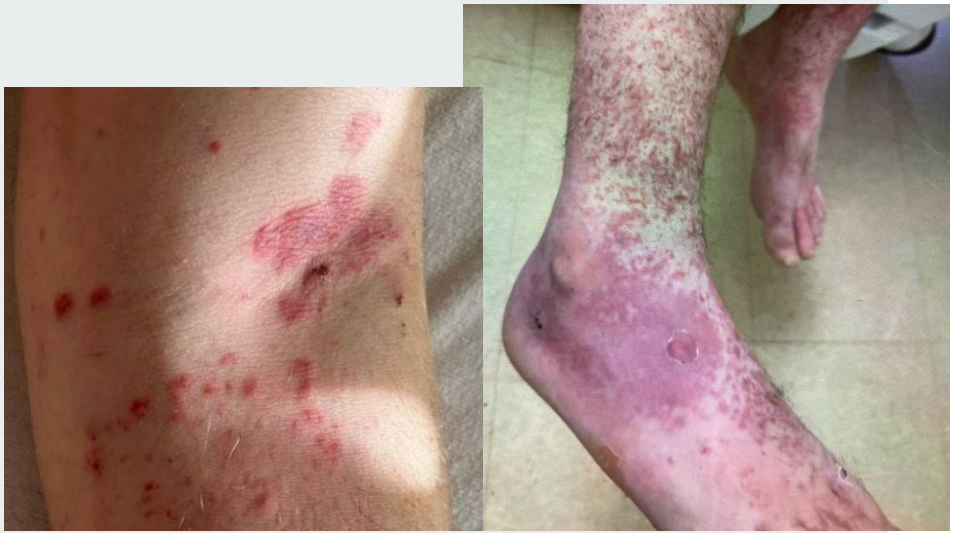
What was the cause of the vasculitis?



- Identify key **side effects of beta-lactams**
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- Define **acute HCV** infection and recognize the appropriate **workup**
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Vasculitis: Patient's results

SKIN PUNCH BIOPSY: Superficial perivascular neutrophil-rich dermatitis, suggestive of an early phase of leukocytoclastic (aka hypersensitivity) vasculitis

Examination of multiple levels reveals features suggestive but not fully diagnostic of leukocytoclastic vasculitis. Fibrinoid degeneration of the blood vessel wall (fibrinoid necrosis) is NOT observed; however, there is a mildly dense predominantly lymphocytic, but neutrophil-rich with scattered eosinophils superficial perivascular infiltrate and areas of focal nuclear dust (karyorrhexis) and erythrocyte extravasation. GMS, Gram, and PAS stain are negative for microorganisms.

Leukocytoclastic vasculitis is a time-dependent process that initially presents as lymphocyte-predominant perivasculitis, and fully developed pathologic changes may not have evolved fully. The histologic differential diagnosis would include a dermal hypersensitivity reaction, such as urticaria. Clinical correlation is recommended.

SKIN BIOPSY, FOR DIRECT IMMUNOFLUORESCENCE: Entirely negative immunofluorescence exam

By immunofluorescence microscopy; direct immunofluorescence with conjugates including anti-IgG, anti-IgA, anti-IgM, anti-C3, and anti-fibrinogen is negative for immunoreactants.

Vasculitis: Overview of classification

Small-vessel vasculitis

ANCA associated
GPA, eosinophilic GPA
Microscopic polyangiitis

Immune complex
Anti-GBM
IgA (HSP)
Cryoglobulinemia

Medium-vessel vasculitis
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)

Large-vessel vasculitis
Giant cell arteritis (GCA)
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Variable-vessel vasculitis
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Others

Vasculitis associated with systemic disease
Rheumatoid vasculitis, lupus vasculitis, IBD vasculitis, others

Vasculitis associated with probable etiology
HCV cryoglobulinemia
HBV, syphilis, cancer
Drug associated ANCA vasculitis
Drug associated immune complex
Others

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Leukocytoclastic vasculitis (LCV) (hypersensitivity vasculitis)

- Histopathologic term, not a diagnosis
- Inflammatory infiltrate of small vessels composed of neutrophils

Vasculitis: Cryoglobulinemia

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GPA, eosinophilic GPA
Microscopic polyangiitis

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Vasculitis: Cryoglobulinemia

- Main association with cryoglobulinemic vasculitis is **chronic**[2.4] **HCV infection** or **connective tissue diseases**
  - Causes a **mixed cryoglobulinemia syndrome**
- **B-cell hyperactivation** → expansion of cryoglobulin-producing B-cell clones → Aggregation of immunoglobulins
- 80% of patients present with triad of **purpura, weakness, and arthralgia** [2.4]

Skin Biopsy: Leukocytoclastic vasculitis

Immunofluorescence: deposits of IgM, IgG, and/or C3 complement

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Drug associated
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Skin Biopsy: Leukocytoclastic vasculitis

Immunofluorescence: deposits of IgM, IgG, and/or C3 complement

Unlikely in our case

- Serum cryoglobulins negative
- No deposits on IF
- Typically have other manifestations too
- Acute HCV is uncommon cause (most cases are in chronic HCV)

Vasculitis: Antibiotic associated

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GPA, eosinophilic GPA
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Immune complex
Anti-GBM
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Vasculitis: Antibiotic associated

- **Drug induced leukocytoclastic vasculitis** account for 10% of all vasculitis cases
- **Antibiotics** (quinolones, beta lactams, sulfas) **are common causes**
- Skin lesions (**palpable purpura**) begins **7-21 days after exposure**
- Mechanism unclear, but antibiotic can act as haptens [2.2, 2.4]
  - Most cases are **type III hypersensitivity** (immune complex) reaction
  - Uncommon to see ANCA associated drug induced from antibiotics (versus hydralazine)
- **Half of patients** may have **systemic manifestations** (most often renal)

Skin Biopsy: Leukocytoclastic vasculitis

Immunofluorescence: deposits of IgM, IgG, and/or C3 complement; only seen early on (**within 48h of rash**)

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Skin Biopsy: Leukocytoclastic vasculitis

Immunofluorescence: deposits of IgM, IgG, and/or C3 complement; only seen early on (**within 48h of rash**)

***Less likely* in our case**
- Rash developed **4 days** after getting antibiotics
- No further rash on Ancef

Vasculitis: Endocarditis

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ANCA associated
GPA, eosinophilic GPA
Microscopic polyangiitis

Immune complex
Anti-GBM
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Others

Vasculitis associated with systemic disease
Rheumatoid vasculitis, lupus vasculitis, IBD vasculitis, others

Vasculitis associated with probable etiology
~~HCV cryoglobulinemia~~
HBV, syphilis, cancer
Drug associated ANCA vasculitis
~~Drug associated immune complex~~
Others (endocarditis)

Vasculitis: Endocarditis

- Tricky because endocarditis' embolic phenomenon can **mimic vasculitis**, but endocarditis can also rarely **cause vasculitis itself**
- In one review [2.5], higher risk for **immunologic phenomenon in subacute endocarditis** (atypical pathogen, right sided)
- Variable mechanisms
  - Most often immune complex mediated
    - Even cryoglobulinemic vasculitis (in a patient with chronic HCV [2.5])
  - Some reports of inducing autoantibody formation (ANCA vasculitis) [2.2]
- Often diagnosed by **improvement of vasculitis with treatment of endocarditis** (including valve replacement)

Skin Biopsy: Leukocytoclastic vasculitis or septic emboli

Immunofluorescence: deposits of IgM, IgG, and/or C3 complement if immune complex mediated, otherwise nonspecific [2.3]

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***Possible* in our case**
- Prompt resolution of rash with antibiotics
- Doesn't *have* to be mediated by immune complexes (so IF could be negative)

Learning points & take aways

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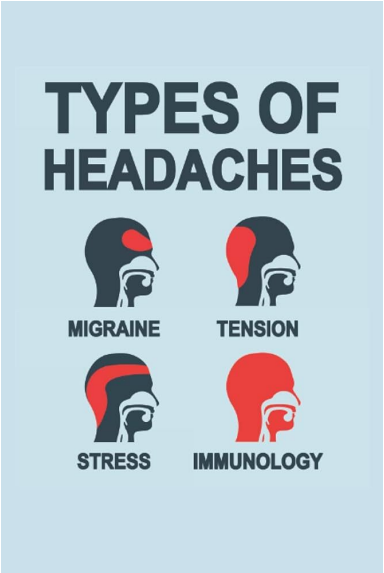
- ✓ Abnormal labs occur frequently during OPAT, but **labs alone rarely drive a change in therapy**
  - ❖ **Antibiotic associated neutropenia** is common (2.2% - 34%), often occurring in the **third week of therapy**. Most patients will be **asymptomatic**
  - ❖ **Cephalosporin induced liver injury** is most often a **mild cholestatic elevation** occurring **1-4 weeks** after the first dose
  - ❖ **Eosinophilia** should **heighten awareness for possible hypersensitivity reactions**, particularly when it occurs early in the treatment course (in the **first two weeks**)
- ✓ **HCV's eclipse period** is **~2 weeks**; **window period** is **2-6 months**
  - ❖ **LFT abnormalities often occur before seroconversion**, so should obtain PCR
- ✓ **Vasculitis is complicated**; biopsy alone may not reveal the diagnosis so clinical context is key
  - ❖ **Endocarditis**, particularly **subacute endocarditis**, may cause an **immune complex mediated LCV**, though can also cause **cryoglobulinemic or ANCA vasculitis**



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