Being right
(for the wrong reasons)

CLINID conference
Hunter Ratliff
06/04/2026

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

Shortcuts

Case 1: Start
Case 2: Start
Inadvertent treatment for lyme?

CSF mNGS | Limitations

Case #1

Case 1: HPI

A **32 y/o F** with PMH including seasonal allergies, multiple sclerosis (on Cladribine) w/ prior right optic neuritis p/w **new intractable migraines**.

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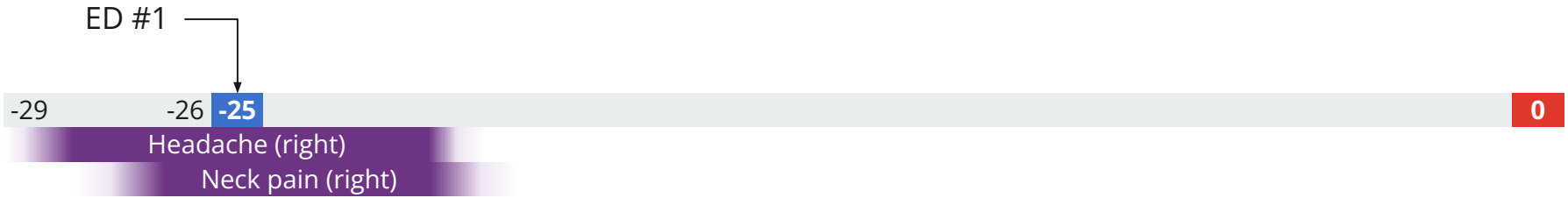
ED (-25d) - **New neck pain** of lateral right neck. Been having a few days of **right sided throbbing headache** as well. CT normal, discharged



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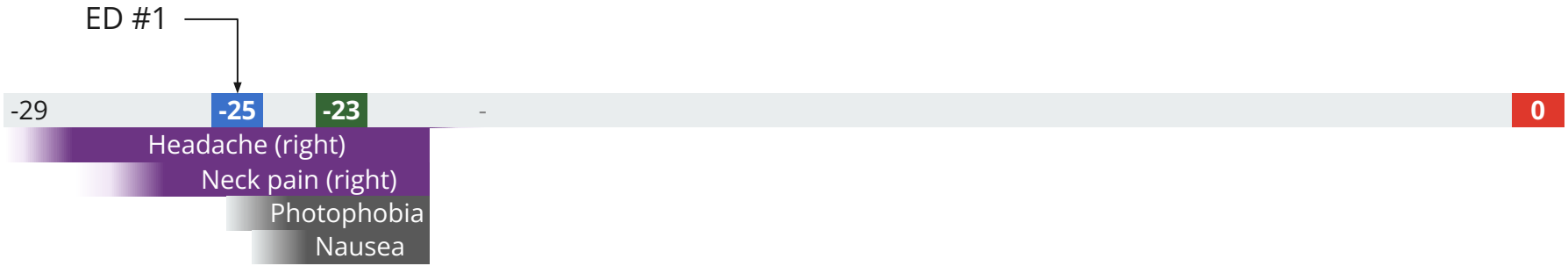

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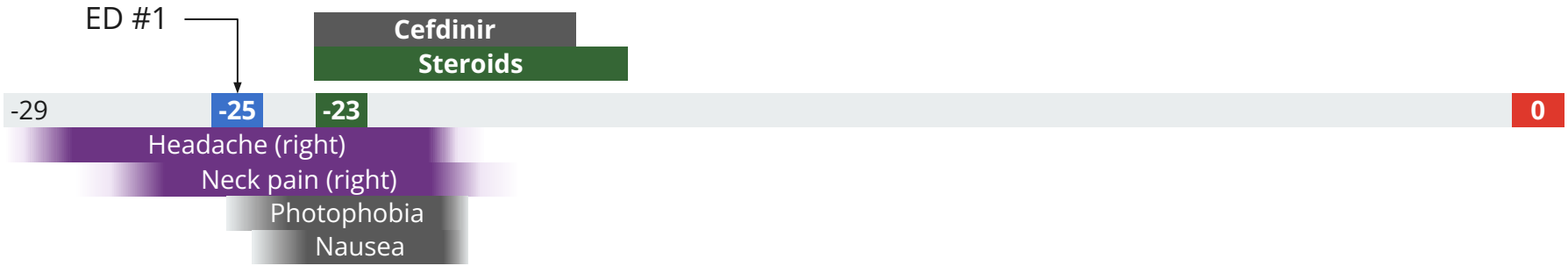

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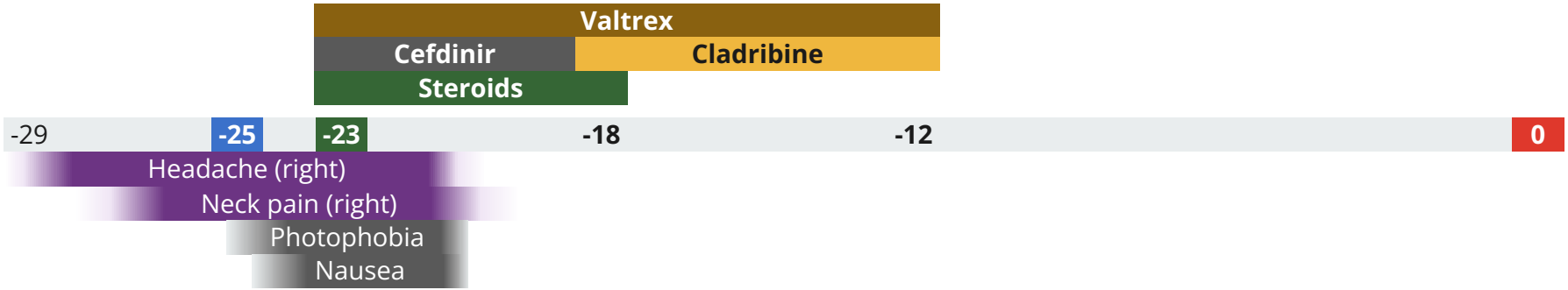
➔ Pharm starts valtrex secondary PPx (her oral HSV tends to recur with her Cladribine)



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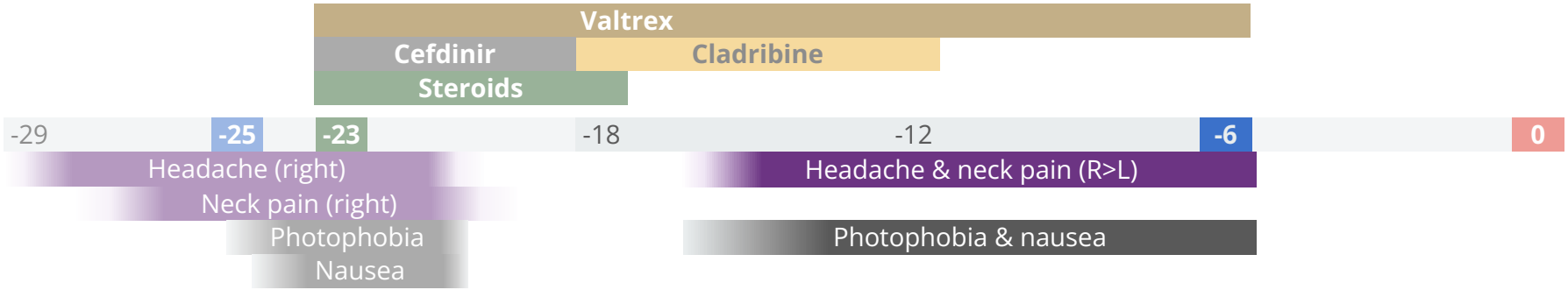

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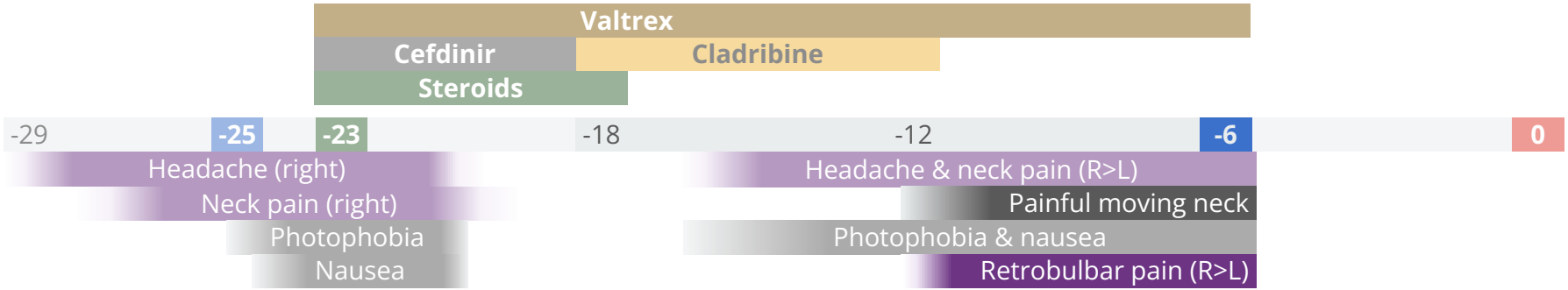

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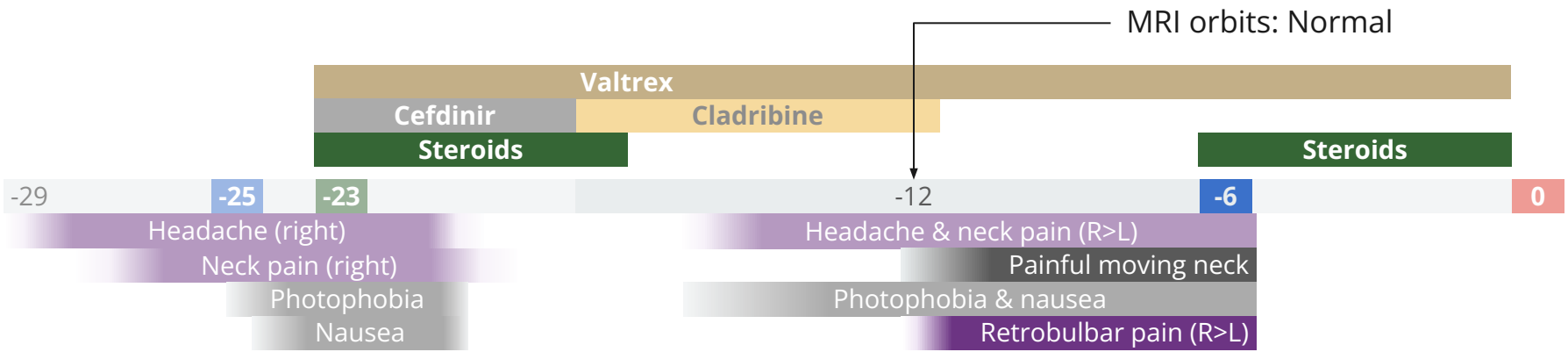

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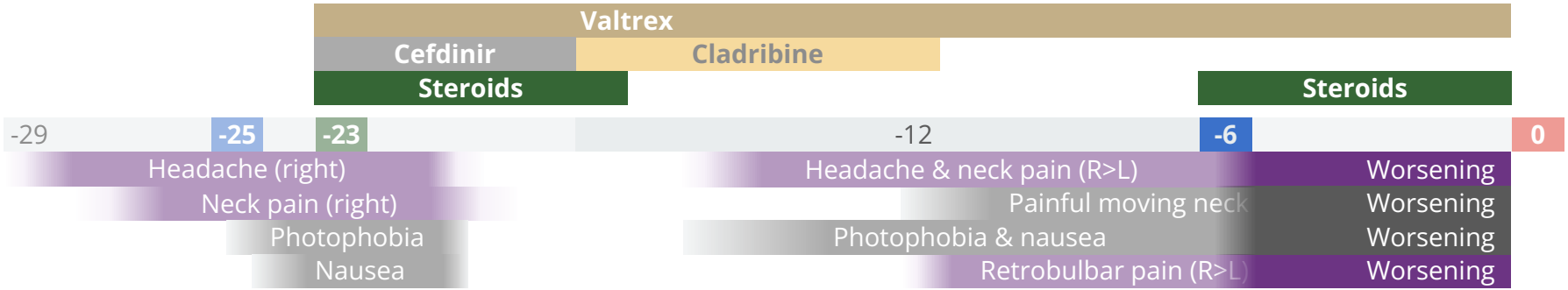
➔ This time, **she does not get better** / worsens



Case 1: Physical exam

BP	137/80	**Pulse**	99	**SpO2**	99 %
Temp	36.4 °C (97.5 °F)	**RR**	18	**BMI**	28 kg/m^2
General	Alert and oriented, NAD, pleasant and interactive				
HEENT	NCAT; trachea appears midline, no gross LAD; EOMI, no ulcers				
Resp	Normal respiratory effort, symmetric chest rise				
CV	RRR; extremities perfused				
GI	Non-distended; no TTP				
Extremities	No clubbing, cyanosis, or edema				
Neuro/MSK	Moves extremities, **no deficits**				
Psych	Normal mood; appropriate affect				

Case 1: Labs

CBC	Result
WBC	3.1
Hgb	11.2
Platelets	191
Neut %	69
Lymph #	370
Eos %	0%

Chem7	Result
Na	140
K	3.8
HCO3	23
BUN	9
Cr	0.8

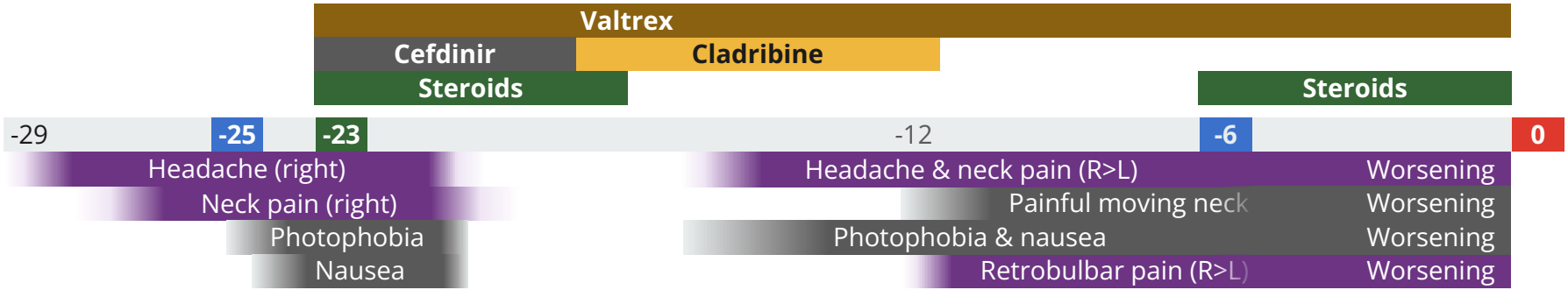
LFTs	Result
AST	11
ALT	9
Alk Phos	41
Bili	0.8
Albumin	3.3

Case 1: Summary

A **32 y/o F** with PMH including seasonal allergies, multiple sclerosis (on Cladribine) w/ prior right optic neuritis p/w **status migrainosus**

CBC	
WBC	**3.1**
Hgb	11.2
Platelets	191
Lymph #	**370**

Has had progressively worsening **headache** with **meningeal signs** (but no fevers or constitutional sx) for the **past 4 weeks**, **progressively worsening** with no improvement aside from transient improvement with a course of **steroids/cefdinir**, but *only* the first time around



Case 1: Social history, exposures, & risk factors

Geographic & Travel	• Lives in WV w/ partner & young kid • No recent travel, never outside of the country
Occupational	• **Science educator** (quite knowledgeable) • Partner works in a **correctional facility**, but reportedly normal TB testing
Animals	• Only (exclusively indoor) **cat**, no birds
Exposures	

Case 1: Social history, exposures, & risk factors

Geographic & Travel	• Lives in WV w/ partner & young kid • No recent travel, never outside of the country
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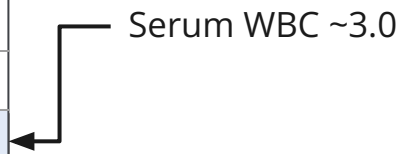
Animals	• Only (exclusively indoor) **cat**, no birds
Exposures	• Spends a fair amount of **time outdoors** in the yard; not in long grass or the woods • Has **seen ticks this season**, **none were embedded** • There is a farm uphill from where she lives…water is **well water** • Some **gardening & soil exposures**

Case 1: Lumbar puncture

Lumbar Puncture	
Opening Pr	22 cm H2O
WBC	**58**
Lymph %	92
RBC	145
Protein	**108**
Glucose	**41**
Serum	
CSF:Serum	
Lactate	**4.1**



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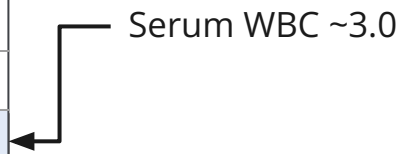

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CSF	Result
Biofire	???
HSV PCR	???
VDRL	???

Serum	Result
HIV	Negative
Syphilis	???

Case 1: MRI brain W/WO

Prior MRI was just MRI of the orbits

MRI brain W/WO: Let my wife explain!

Case 1: MRI brain W/WO

Prior MRI was just MRI of the orbits

MRI brain W/WO: Nonspecific pachymeningeal enhancement. Enhancement along the cisternal segments of bilateral oculomotor & trigeminal nerves, new compared to prior exam. Findings could be seen in the setting of meningitis. No new MS lesions.

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CSF	Result
Biofire	Negative
HSV PCR	Negative
VDRL	Negative
CryptoAg	?

Serum	Result
HIV	Negative
Syphilis	Negative
Lyme	?
Tick panel	?
QuantGold	?

Case 1: Lumbar puncture

Right sided Bell's palsy develops 12-24 hours before tick screening returns

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CSF	Result
Biofire	Negative
HSV PCR	Negative
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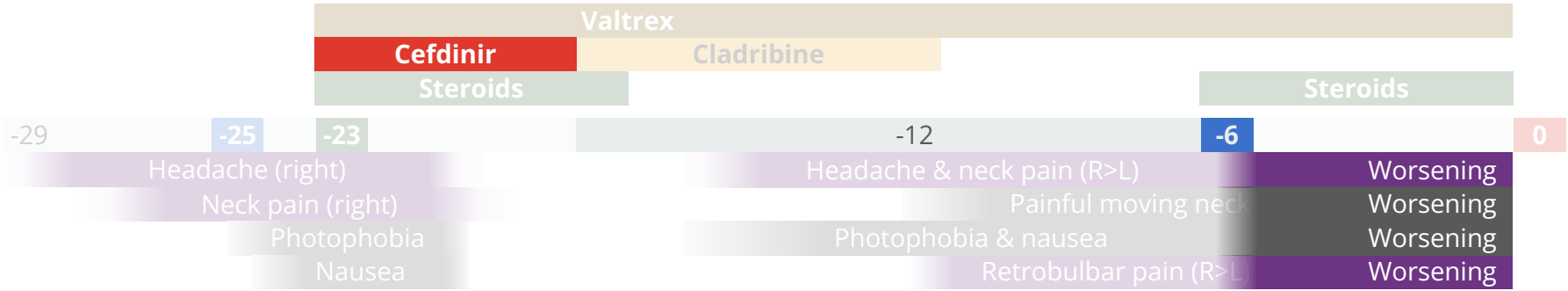
Serum	Result
HIV	Negative
Syphilis	Negative
Lyme	**Positive**
Tick panel	Negative
QuantGold	Negative

Case 1: Revisiting the history

A **32 y/o F** with PMH including seasonal allergies, multiple sclerosis (on Cladribine) w/ prior right optic neuritis p/w **new intractable migraines**.

- **Clinic** (-23d) - Noted to have **nausea** & mild **photophobia**; left ear feels full → **medrol dose pack** and **Cefdinir**
- **ED #2** (-6d) - Exam & labs reassuring (and recent MRI orbits okay), so they send home with **steroids** (but **no antibiotics**)



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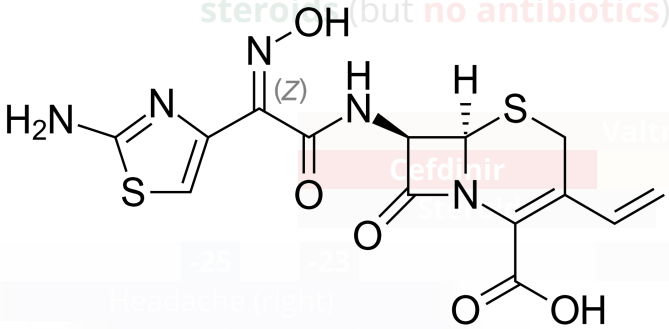
- **Clinic** (-23d) - Noted to hav
  pack and **Cefdinir**
- **ED #2** (-6d) - Exam & labs r
  steroids (but **no antibiotics**)

INTERVAL EVENTS / SUBJECTIVE
No events overnight, patient seen at bedside accompanied by spouse. Headache a little better. Says she was **feeling better** while receiving **IV antibiotic** that started with "cefe-" [**cefepime**]



Cefdinir (looks a lot like ceftriaxone)

Valtrex
Cefdinir
Cladribine
Steroids
-29 -25 -23 -12 -6 0
Headache (right)
Neck pain (right)
Nausea
Headache & neck pain (R>L) Worsening
Painful moving neck Worsening
Photophobia & nausea Worsening
Retrobulbar pain (R>L) Worsening

Inadvertent treatment for lyme?

Inadvertent treatment for Lyme

2006 IDSA guidelines [1]

In contrast to the:

- **second-generation cephalosporin cefuroxime** and
- **certain third-generation cephalosporins** (e.g., **ceftriaxone**) [**125**]...

2nd gen
(cefuroxime)

3rd gen
(ceftriaxone)

Inadvertent treatment for Lyme

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- **certain third-generation cephalosporins** (e.g., **ceftriaxone**) [125]...

first-generation cephalosporins, such as cephalexin [133], are inactive in vitro against B. burgdorferi and are ineffective clinically

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(Keflex)

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1st gen
(Keflex)

2nd gen
(cefuroxime)

3rd gen
(ceftriaxone)

3rd gen
(cefdinir / Omnicef)

Lyme & oral cephalosporins [2]

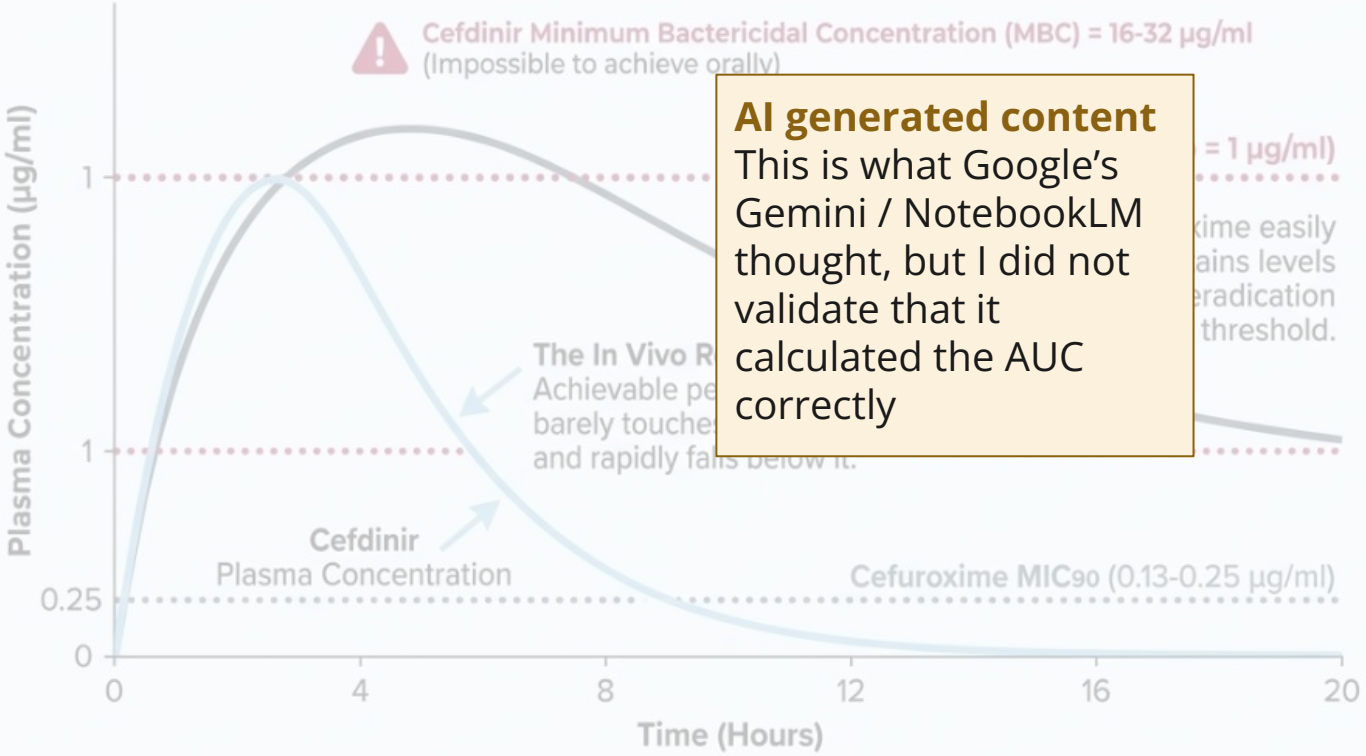
In vitro study of activity against B. burgdorferi

	Cephalosporin	Gen	MIC_{90} (mg/L)
✓	Ceftriaxone (Rocephin)	3rd	0.06
✓	Cefuroxime (Ceftin)	2nd	0.25
?	**Cefdinir** (Omnicef) & cefixime	3rd	1.0
	Cefpodoxime (Vantin)	3rd	8
	Cefaclor	2nd	16
	Ceftibuten	3rd	32

However… did not look at bioavailability, tissue distribution, etc

INTERVAL EVENTS / SUBJECTIVE
Says she was **feeling better** while receiving IV antibiotic that **started with "cefe-"**

Cefdinir: The Gap Between Lab Susceptibility and Clinical Reality



AI generated content
This is what Google's Gemini / NotebookLM thought, but I did not validate that it calculated the AUC correctly

Insight: In vitro susceptibility means nothing if achievable plasma concentrations cannot sustain eradication levels over time.

What about cefepime? [3]

An even older in vitro study (1999, 3 years before LOTR two towers was released)

- Investigating a new drug (everninomicin) that only made it to phase III
- But also compared it to other new-er antibiotics (cefepime, linezolid, Merrem)

Cefepime had activity, but **not great**

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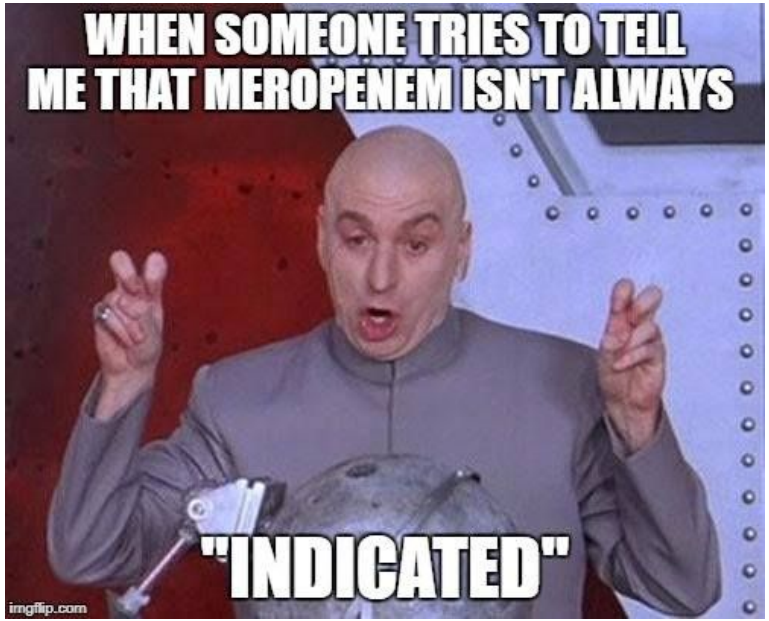


However, **meropenem had excellent activity**

- Time-kill (@ x2 MIC) was **comparable to ceftriaxone**
- Better than doxycycline

Case #2

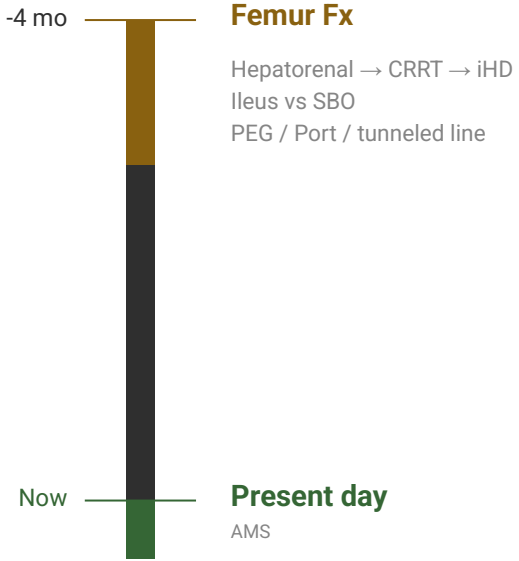
Case 2: HPI

A **53 y/o F** with PMH including decompensated NASH cirrhosis (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **GI symptoms & AMS** from SNF

Case 2: HPI - prior hospital stay

A **53 y/o F** with PMH including decompensated NASH cirrhosis (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **GI symptoms & AMS** from SNF

- Four months ago, slipped on some ice at home and broke left femur
  - Uneventful ORIF
- Then had AKI → needed trialysis CVC for possible iHD
  - Ileus vs possible SBO
- During line placement, had emesis & aspiration → intubated and sent to MICU
  - Started on CRRT



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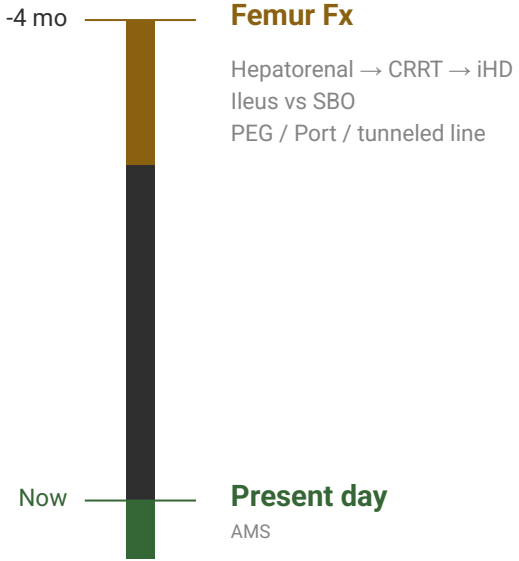
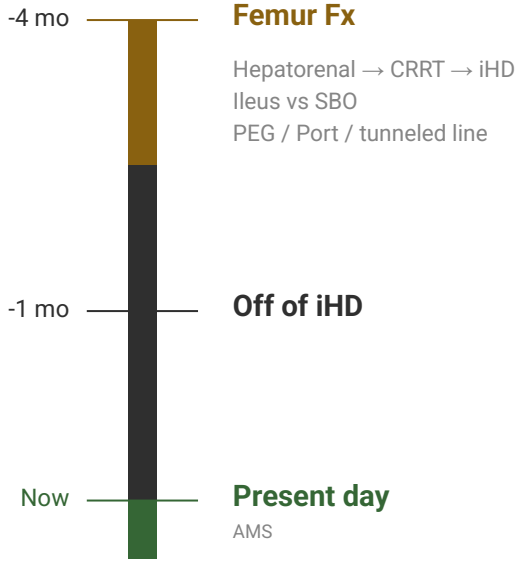
- SBO: Failed swallow studies → got PEG
- Nutrition: was on TPN → port placed (for TPN)
- AKI/HRS: CRRT → iHD
  - Temp CVC removed → tunneled line placed
- Hepatology stuff: Delisted due to prolonged intubation
  - CT showed new splenic thrombosis (post-op)
- ID stuff: Not really much, treated for aspiration



Case 2: HPI - since last hospital stay

A **53 y/o F** with PMH including decompensated NASH cirrhosis (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **GI symptoms & AMS** from SNF

- Discharged to SNF from that month long admission
- After about 1.5 months, no longer needing HD → tunneled line removed



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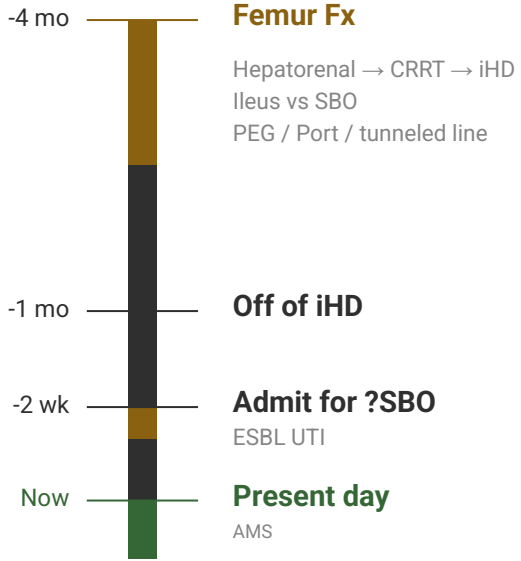
Subsequent admission 2-3 weeks ago for SBO symptoms

- Managed nonoperatively with NG tube
  - ...despite the fact that she already had a PEG tube?
- They got a urine culture...
  - Why did they get a urine culture? Who knows!
  - Grew ESBL E coli → Rx Cipro (until ID Gold says fosfomycin)



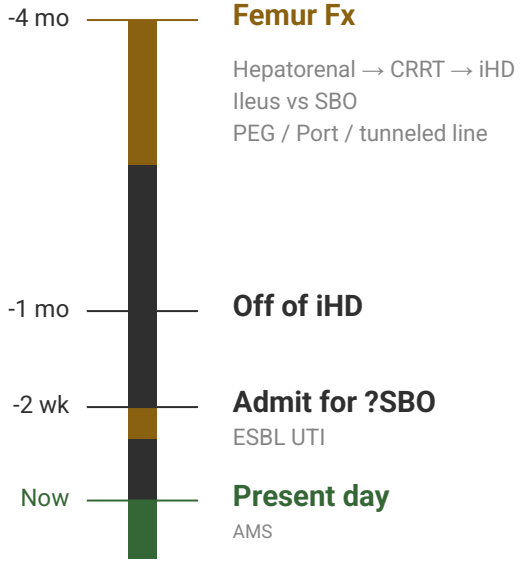
Case 2: HPI - Present admission

A **53 y/o F** with PMH including decompensated NASH cirrhosis (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **GI symptoms & AMS** from SNF

Sent from SNF to OSH by EMS (same OSH as prior admits)

- Periumbilical pain
- Nausea + intractable vomiting
- No diarrhea, dyspnea, fevers, dysuria

Initial H&P not focused much on mentation / neuro, but does note she seems “disoriented” but can respond non-verbally to questions



Case 2: Social history, exposures, & risk factors

Geographic & Travel	
Occupational	
Substance & needles	
Animals	
Exposures	

Unable to obtain

Case 2: Physical exam

BP	145/**102**	**Pulse**	**106**	**SpO2**	96 %
Temp	36.7 °C (98.1 °F)	**RR**	**20**	**BMI**	27 kg/m^2
General	"**mumbling and making no sense**", NAD, vitals reviewed				
HEENT	NCAT; trachea appears midline, **dry mucous membranes**				
Resp	Normal respiratory effort, symmetric chest rise				
CV	RRR; extremities perfused				
GI	**Slight distention**; **periumbilical tenderness** **to palpation**				
Extremities	No clubbing, cyanosis; **1+ BLE edema**				
Neuro/MSK	"**No focal deficit present**"				

Case 2: Labs

CBC	Result
WBC	16.2
Hgb	11.4
Platelets	141
Neut %	87%
Lymph #	700
Eos %	0%

Chem7	Result
Na	136
K	3.6
HCO3	37
BUN	12
Cr	1.18

Unclear baseline, but peak (prior to CRRT last admission) was 2.0

LFTs	Result
AST	18
ALT	14
Alk Phos	111
Bili	3.5

More or less baseline

Case 2: Imaging

CT C/A/P WO:

- Liver: Cirrhotic morphology
- Gallbladder: Surgically absent
- Bowel: PEG tube in the stomach. Air-fluid levels throughout the small intestine
- Bones: Surgical hardware left hip

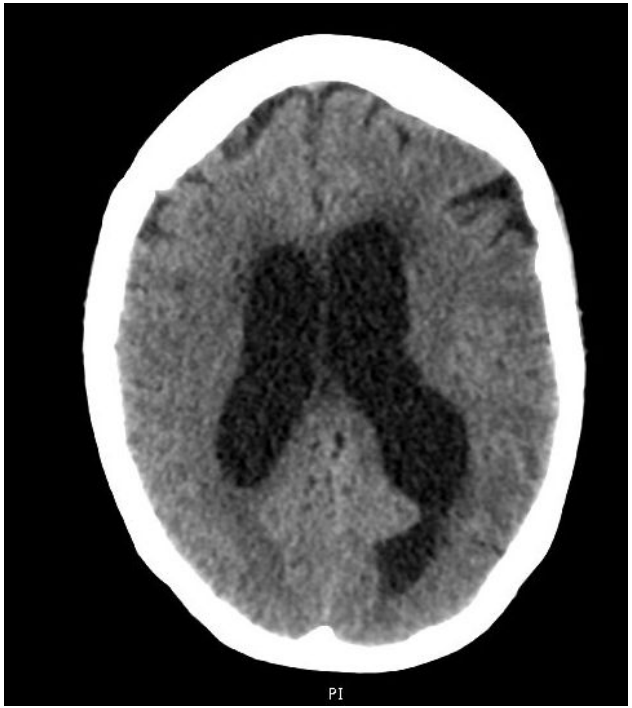
Impression:
Air-fluid levels in the stomach and small bowel. These findings are **nonspecific** but could be due to **an ileus**. An **early or partial small bowel obstruction** is **not excluded**

Case 2: Initial hospital course

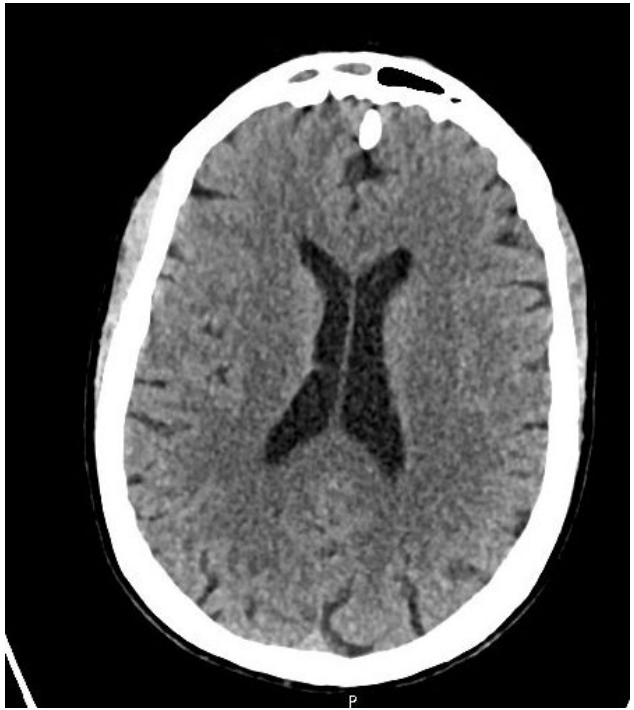
 # Intractable nausea and vomiting
 # Possible ileus
- CT results reviewed
- NPO for now use percutaneous endoscopic gastrostomy tube
- Consult General surgery appreciate recs
- LR 75 mL/HR continuous

The following day
Perhaps **we should get a CT brain**, since this isn't her baseline...

Case 2: CT head

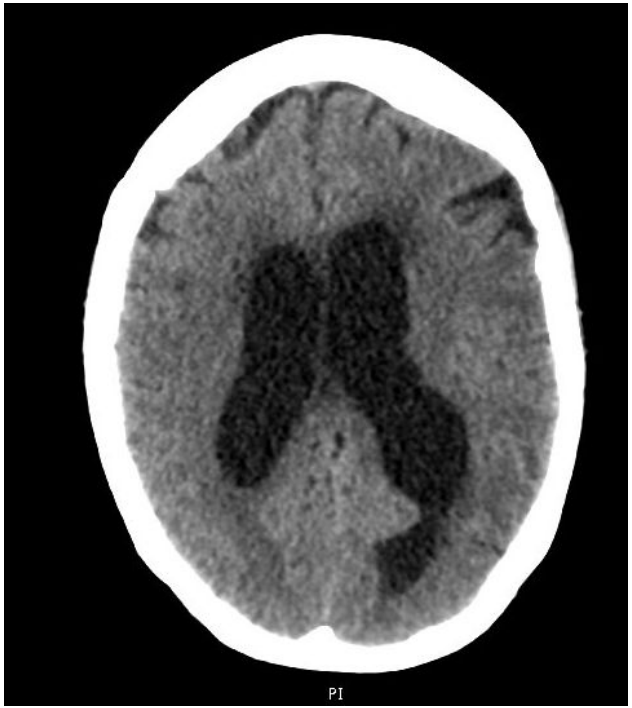


Current admission



Femur fracture admission

Case 2: CT head



Current admission

CT head WO

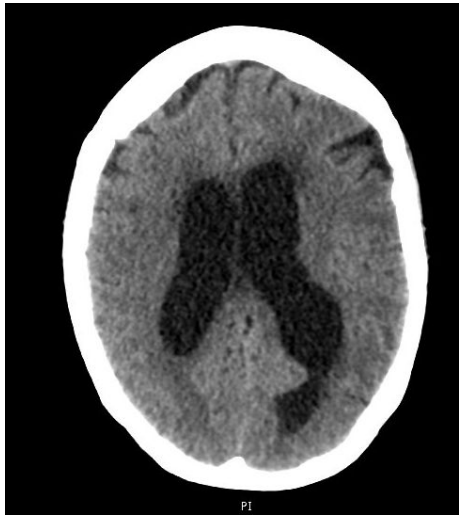
New onset hydrocephalus pattern with probable **subependymal edema** in the periventricular region.

No obvious obstructing mass or intraventricular/intracranial bleed is seen as an etiology on this scan. Differential considerations need to **include the possibility of infectious etiology causing difficulty resorbing CSF**

Case 2: Summary

A **53 y/o F** with PMH including decompensated **NASH cirrhosis** (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **abd pain**, **n/v**, & **AMS** from SNF

Initially thought symptoms were related to intra-abdominal process, but once they figured out her **mental status was not at baseline** → discovered **CSF flow was also not at baseline**



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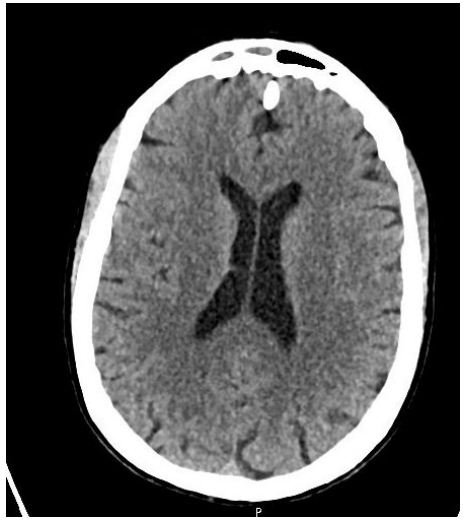


Femur fracture admission

CBC	
WBC	16.2
Hgb	11.4
Platelets	141
Neut %	87%
Lymph #	700
Eos %	0%

Chem7	
Na	136
K	3.6
HCO3	37
BUN	12
Cr	1.18

LFTs	
AST	18
ALT	14
Alk Phos	111
Bili	3.5

Case 2: Ruby transfer

- Admitted to NCCU
- Overnight IRRAflow placed
- MRI brain ordered (more on this later)
- CSF studies return…

Started **CNS vanco** & **ceftriaxone**
…but **no blood cultures**
…or droplet precautions

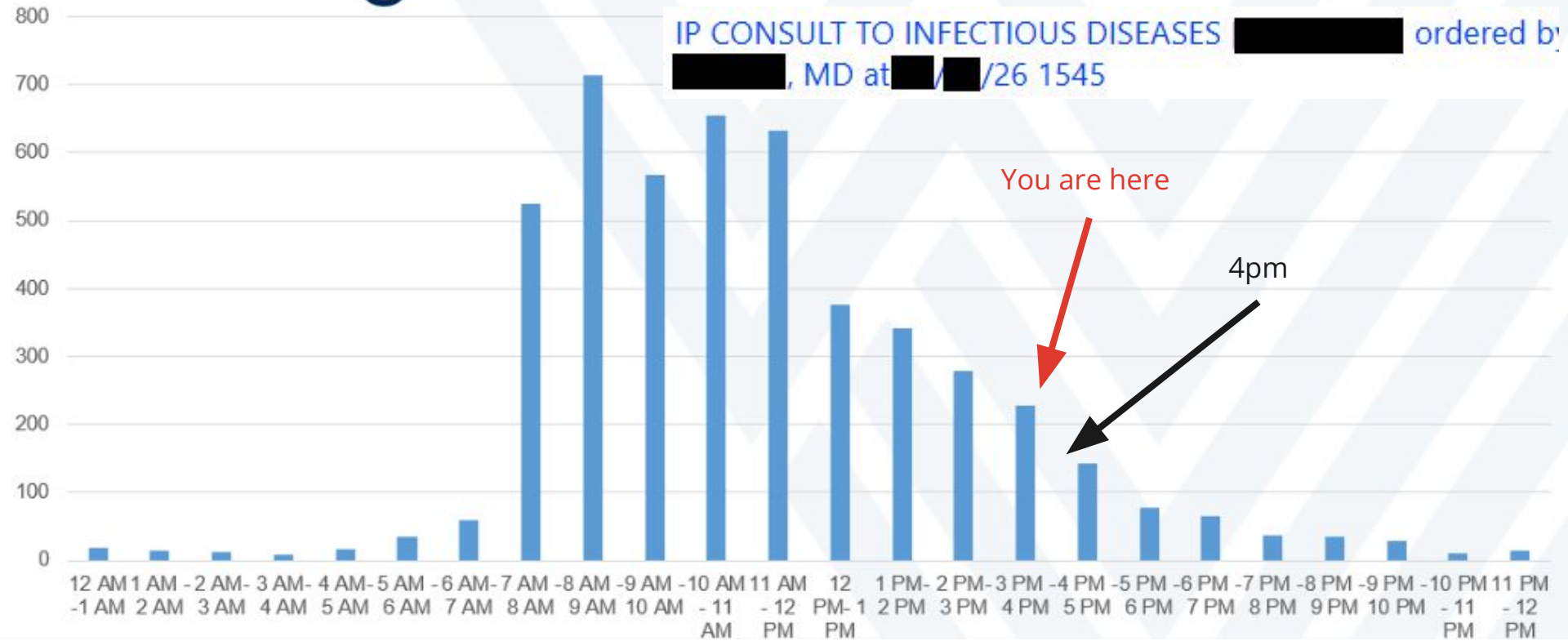
CSF	Result
VZV PCR	…
HSV PCR	…
S pneumo Ag	…
CryptoAg	…
Biofire	…

IRRAflow CSF	
Opening Pr	???
WBC	**86**
Neut %	75
RBC	367
Protein	**145**
Glucose	**56**
Serum	166
CSF:Serum	**0.33**

" Initial pressure was low"

Serum	Result
HIV	Negative
HCV PCR	TND

Timing of ID Consult Order



Case 2: MRI brain

Let my wife explain it

Case 2: MRI brain W/WO

IMPRESSION:

- **Purulent fluid** layering within the occipital horns **of the lateral ventricles**, with *small amount of hemorrhage* in the right lateral ventricle
  - Stable positioning of right frontal approach EVD
- Abnormal **leptomeningeal enhancement** along the:
  - **Brainstem** - medulla & pons
  - **Right cerebellum**
  - **Cranial nerves** - right oculomotor, R abducens, R CN ⅞ complex
- Nonsuppression of CSF signal on FLAIR in the **basal cisterns** (interpeduncular & prepontine) and within the cerebral sulci

Findings are concerning for **ventriculitis and meningitis**

Case 2: CSF studies & initial ID plan

CSF	Result
VZV PCR	…
HSV PCR	…
S pneumo Ag	…
CryptoAg	…
Biofire	…

Case 2: CSF studies & initial ID plan

- Add ampicillin
- Droplet isolation
- Send CSF biofire
  - Not validated for ventricular fluid
- Follow cultures
  - However, patient got a dose of ertapenem at OSH (ESBL “UTI”)

CSF	Result
VZV PCR	Negative
HSV PCR	Negative
S pneumo Ag	Negative
CryptoAg	Negative
Biofire	???

Case 2: The next 48 hours

Remains afebrile (but cirrhosis)

Mental status not better

Starts getting very weird nystag

Next steps?

CSF	Day 1	Day 3
EVD mode	Drain only	Irrigation
WBC	**86**	**160**
Neut %	75%	83%
RBC	367	13
Protein	**145**	**18**
Glucose	**56**	**32**
Routine Cx	NG@2D	G/S neg
Fungal Cx	NG@2D	…
AFB Cx	Smear (-)	…

Case 2: patience is a virtue

Apparently mNGS does increase diagnostic yield…

…CSF cultures finally started growing the day after we sent the expensive test

Case 2: The results

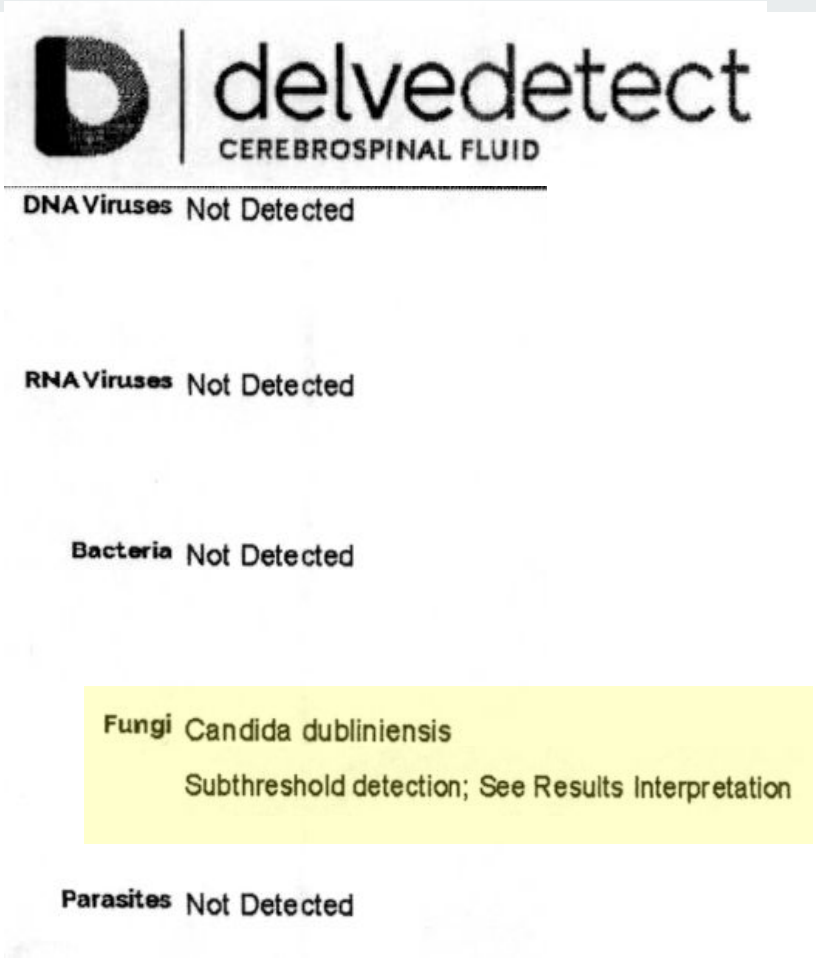
CSF culture: <5 Colonies **Candida dubliniensis**

- 5-FC: 0.06 (S)
- Flucon: 0.50 (S)

Reads aligning to Candida dubliniensis were **identified at a subthreshold level**, below that for formal reporting thresholds.

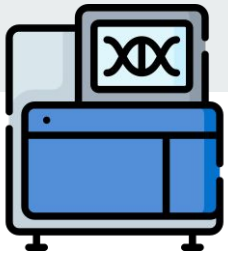
As a commensal organism of human flora, this detection may represent environmental or mucocutaneous contamination. Clinical correlation is recommended.

SPECIMEN NOTES
Sample contains high DNA background, there is decreased sensitivity for detection of DNA viruses, bacteria, fungi, and parasites.



mNGS

Alphabet soup of molecular testing [7]



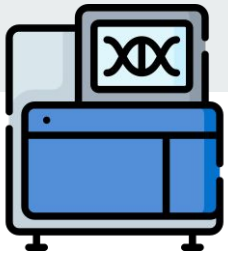
Targeted PCR (singleplex): Targets specific nucleic acid sequences using primers for that pathogen

- Examples: HSV or VZV PCR
- Pros: Cheap, often done in house
- Cons: Limited to single pathogen, so you must be explicit in your DDx based on clinic or epidemiologic history

PCR panel (multiplex): Amplifies two or more target sequences (in the same reaction) using multiple primers

- Examples: Biofire
- Pros: Often done in house, not as expensive as the other tests talked about here
- Cons: Culprit must be on the panel (e.g. if that strain of enterovirus is not on the biofire [source], the test will be negative)

Alphabet soup of molecular testing [7]



Universal PCR (broad range): utilizes primers to amplify and sequence conserved areas of the genome (bacteria=16S rRNA, fungi=28S rRNA)

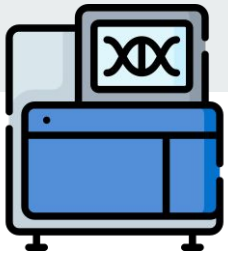
- Pro: Untargeted, broad testing
- Limitations:
  - Does not detect viruses or parasites
  - May fail to identify unusual bacterial/fungal pathogens outside the primers specificity

Traditional PCR
Targeted PCR (HSV, VZV)
Multiplex PCR (Biofire)

Uses primer(s) specific to desired pathogen(s)

Pros: Affordable, faster turn around

Need to know what you're testing for: If it's not on the PCR/panel, won't show up



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Metagenomic NGS (mNGS): sequences any nucleic acid fragments present (including host) → uses bioinformatics to filter out host DNA

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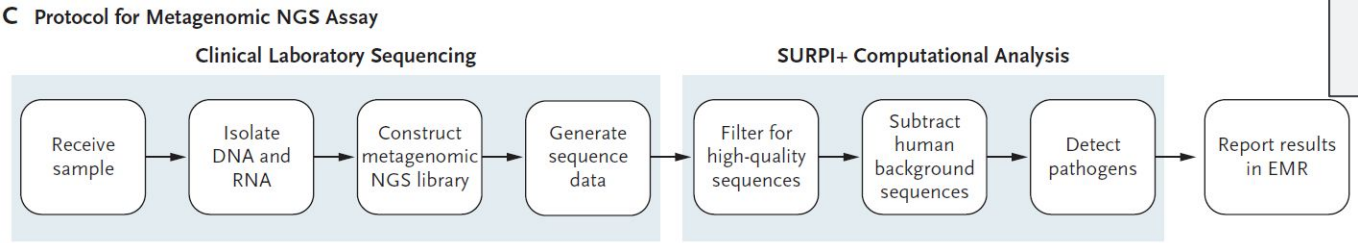

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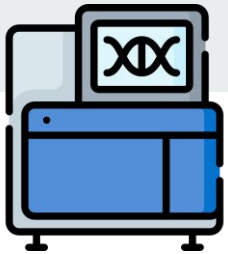

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- Pro: Untargeted, broad testing
- Limitations: No viruses or unusual bacteria/fungi

Metagenomic NGS (mNGS): sequences any nucleic acid fragments present (including host) → uses bioinformatics to filter out host DNA

- Pro: Unbiased (like uPCR), may identify resistance (ESBL)
- Con: Requires the most clinical interpretation, because it's a hypothesis free test
  - Expensive: $2000 - $3500

Traditional PCR
Targeted PCR (HSV, VZV)
Multiplex PCR (Biofire)

Uses primer(s) specific to desired pathogen(s)

Pros: Affordable, faster turn around

Need to know what you're testing for: If it's not on the PCR/panel, won't show up

Does mNGS provide clinical benefit?

Advanced molecular testing has a role **if extensive workup is negative**

- e.g. 2014 case where a teenager had **30+ conventional tests**, only for mNGS to diagnosed neuro-leptospirosis [**7**]

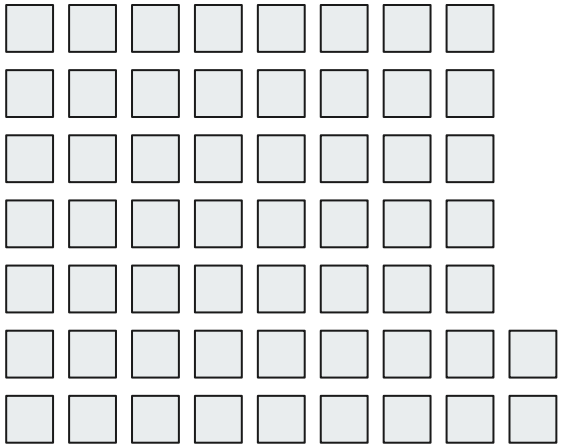
The NEW ENGLAND JOURNAL of MEDICINE

Does mNGS provide clinical benefit? [5]

Landmark multicenter trial (NEJM, 2019)

- **204 adult & pediatric patients** enrolled, who were pretty ill
  - 49% admitted to ICU
  - 11% mortality

- Conventional &/or mNGS diagnosed 58 CNS infections



58 CNS infections diagnosed

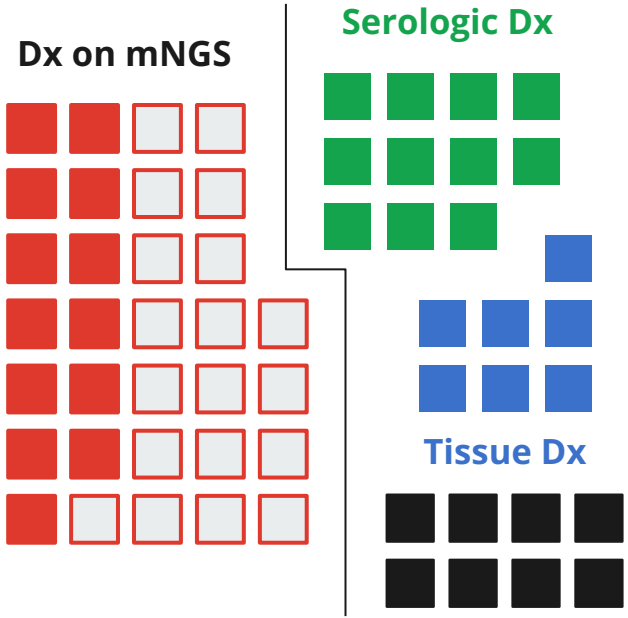
The NEW ENGLAND JOURNAL of MEDICINE

Does mNGS provide clinical benefit? [5]

Landmark multicenter trial (NEJM, 2019)

204 patients, **58 CNS infections**

- **55%** (n=32) had **mNGS diagnosis**
  - **22%** (n=13) were only from **mNGS**
  - 33% on both mNGS & conventional
- Of the 26 infections (45%) not detected on mNGS
  - **19%** (n=11) from **serologic testing**
  - **12%** (n=7) from **tissue Dx**
  - **14%** (n=8) presumably diagnosed from CSF



More recently out of China [9]

Single institution retrospective review (June 2022 - March 2024)

Inclusion / exclusion:

- Patients suspected of having possible encephalitis meningoencephalitis (n=285)
- Had a lumbar puncture
- Got **antibiotics before LP**
- Exclude: No definitive diagnosis (n=22)

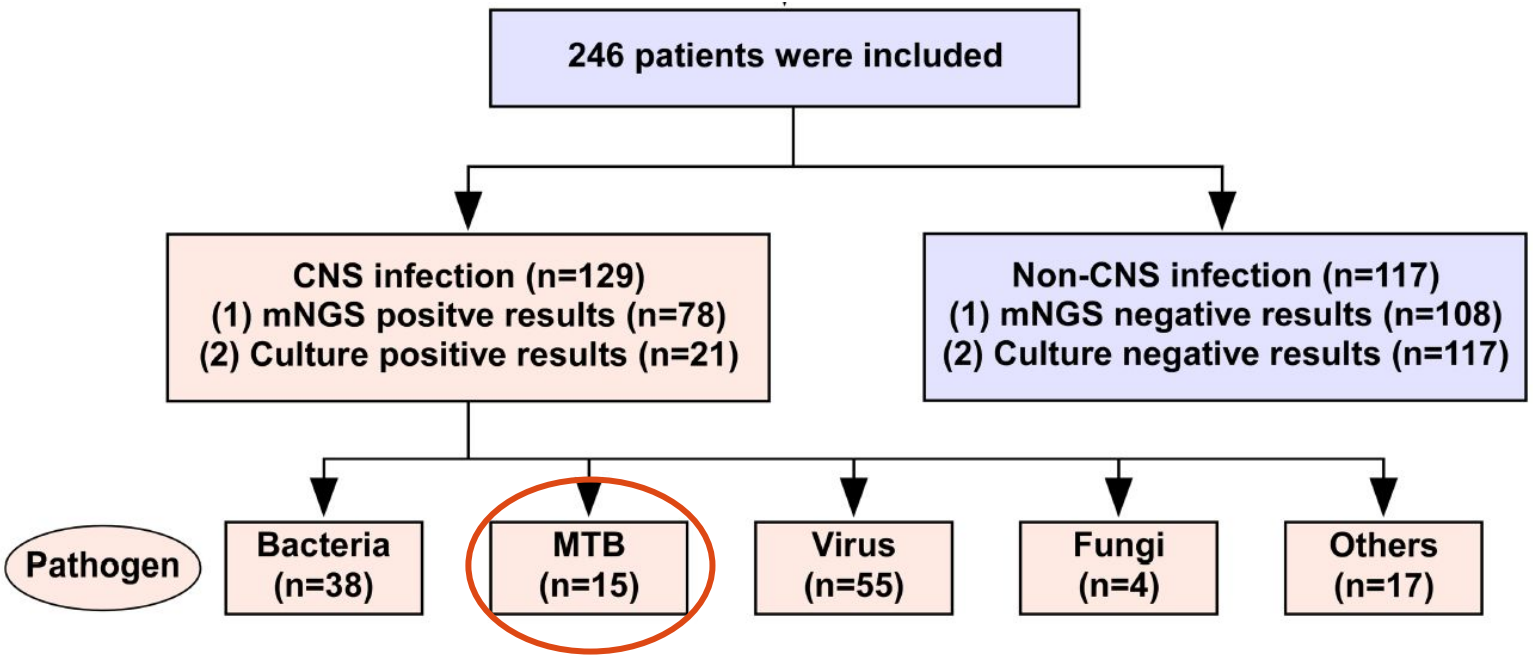
Defining "definitive diagnosis"

Consensus of 3 senior neurologists based on predefined criteria including:

1. Clinical presentation
2. CSF analysis
3. Cultures
4. Conventional molecular testing
    - Serologies
    - Antibody indices
    - PCR (targeted or broad range)
5. Response to therapy

More recently out of China [9]

Single institution retrospective review (June 2022 - March 2024)



More recently out of China [9]

frontiers in Microbiology

mNGS Diagnosed
(and cultures missed)

- Streptococcus pneumoniae (x2)
- Acinetobacter spp (x2)
- Pseudomonas aeruginosa
- Cryptococcus neoformans
- Aspergillus flavus
- Legionella cincinnatiensis

Cultures Grew
(with negative mNGS)

- Staphylococcus epidermidis
- Staphylococcus hominis
- Staphylococcus capitis

More recently out of China [9]

Concordance between “consensus definitive diagnosis” and…

- **mNGS**: 73.2%
- **Conventional**: 61%
- **Culture alone**: 54.1%

Concordance with definitive diagnosis

	mNGS	Culture	Conventional
Fungal	**100%** (4/4)	50% (2/4)	75% (3/4)
MTB	**46.7%** (7/15)	N/A	**26.7%** (4/15)
Overall	60.5% (78/129)	28.8% (17/59)	42.6% (55/129)

More recently out of China [9]

Concordance between "consensus definitive diagnosis" and...

- **mNGS**: 73.2%
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- **Culture alone**: 54.1%

Cut for time [6]

A separate study from UCSF (done in **Ugandan adults** w/ **HIV**) used **mNGS** and **machine learning** to distinguish between TB meningitis & it's mimics

- Sensitivity: 89%
- Specificity: 87%

	mNGS	Culture	Conventional
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Mayo clinic review [8]

Mayo clinic did a retrospective review after using mNGS on CSF (n = 210 adults)

- The most interesting results are in the **69 patients** where suspected neurologic infection **was top of the DDx**
  - 19 patients tested positive, **63%** of whom were **diagnosed on mNGS only**
  - Sensitivity of 64.3%

Variable	Positive (n = 25)	Negative (n = 193)	*P* Value
Reason for ordering MSCSF (%)	…	…	< .001
Suspected neuroinfection	21 (84)	48 (25)	
Other diagnosis more likely	3 (12)	137 (71)	
Repeat MSCSF testing	1 (4)	7 (4)	
Other	0 (0)	1 (1)	

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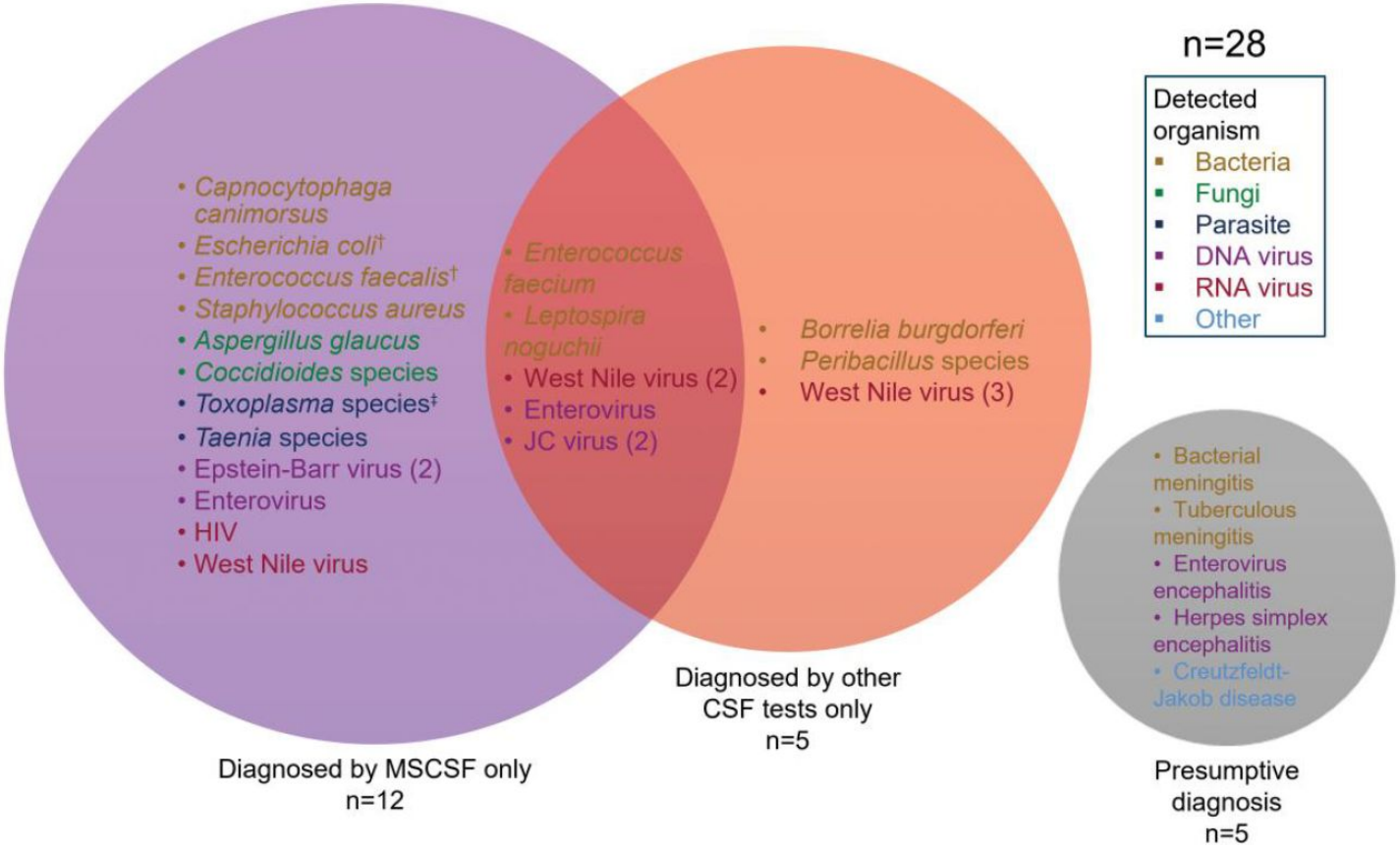
Odds of positive test

- Clinically **high pretest suspicion** of infection **OR=20.1** (5.8-70.5)
- **Immunosuppression** **OR=3.5** (1.4 - 8.9)
- Antibiotics before LP OR=4.4 (1.7 - 11.3)

Mayo clinic review [8]



Mayo clinic review [8]

...but **most of Mayo's testing** (**64%**) was when ***some other diagnosis*** **was more likely**

- This probably isn't the most **cost effective**, right?

Variable	Positive (n = 25)	Negative (n = 193)	*P* Value
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Ruling out infection [4]

- Used a retrospective cohort (2010-2017) of patients diagnosed with either:
  - CNS infections or
  - Autoimmune encephalitis
- Used these patients to **model how mNGS** could have **changed management**
  - Excluded: patients who had a diagnosis in <48h or positive Biofire
  - Used Bayesian models to compare routine care --vs-- mNGS sent on the initial LP

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Among the **29 patients** with **confirmed autoimmune encephalitis**, doing upfront mNGS would:

- **Avoid 126** etiologic **tests** (4.3 per patient)
- **Avoided 297 days** of ruling out infection (10.2 per patient)

Ruling out infection [4]

- Used a retrospective
  - Excluded: patient
  - Used Bayesian m

Greatest benefit was autoimmune cohort

- Reduced **infectious testing by 92%** (vs 64% in infectious cohort)
- Reduced **time to diagnosis by 10.2 days** (vs 6.9 days)

Total number avoided (per patient)

	LPs	Etiologic tests	Days saved
DNA virus (n=23)	2 (0.09)	88 (**3.8**)	145 (6.3)
Bacterial (n=16)	12 (**0.75**)	30 (1.9)	144 (**9**)
Fungal (n=7)	3 (**0.49**)	29 (**4.1**)	61 (**8.7**)
Autoimmune (n=29)	2 (0.10)	126 (**4.3**)	297 (**10.2**)

What about cost?

Estimated cost to organization

$100-250

- Lyme IgG, CSF
- West Nile RNA, CSF
- Rabies Ab Screen RFFIT
- Multiple sclerosis profile, serum & CSF

$250-500

- Serum autoimmune & paraneoplastic panel
- AQP4 Ab w/ reflex to titer (serum + CSF)

- **$700**: CSF biofire
- **$850**: MOG Ab w/ reflex titer, CSF
- **$1000**: NMDA receptor antibody test

- **$3000**: MRI brain W/WO

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The literature says DelveDetect runs around $2000 - $3500

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Rabies?
mNGS has diagnosed rabies on the CSF [**10**]

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Limitations with mNGS [7]

Two key principles:

1. Detection requires a pathogen's nucleic acid to be in the CSF
2. Presence of nucleic acid does not necessarily mean it is causing the illness

Limitations with mNGS [7]

Specimen Handling

- Nucleic acid degrades at room temperature, especially neuroinvasive RNA viruses
- Sterile processing to limit contamination

Key principles

1. Pathogen DNA/RNA must be in CSF to be detected
2. Detection of DNA/RNA does not *necessarily* mean it is causing the illness

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Anatomic Factors

- Only tests the CSF, not the entire nervous system
- Expect negative results for walled off or epidural abscesses

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Pathogen Factors

DNA/RNA concentrations fluctuate; use serologies when appropriate

- **Paucicellular infections:** Low loads in neuroborreliosis & neurosyphilis
  - TB is just hard to diagnose, but maybe not with machine learning on host gene expression; see citation [6]
- **Temporal Clearance:** Viral loads peak days before symptom onset in arboviral (e.g. WNV) & tick-borne encephalitis

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Host Factors

Nucleic acid from host cells (WBC, RBC) compete with pathogen nucleic acid during sequencing

- If host response > pathogen abundance (pleocytosis > 200 [5]), may decrease sensitivity
- Perhaps this is why mNGS does better with immunocompromise

The host-response limitation is <u>not</u> present in uPCR (broad range), since they have set primers (16S, 28S)

Key principles

1. Pathogen DNA/RNA must be in CSF to be detected
2. Detection of DNA/RNA does not *necessarily* mean it is causing the illness

Reframing the role of mNGS

"Rather than triaging a narrow set of suspected pathogens based on pretest probability, clinicians now must interpret unbiased sequencing data within the clinical context. In this way, **mNGS redefines the clinician's role—from choosing what to test to *discerning what the findings mean***. Far from replacing it, clinical judgment remains integral to the impact and utility of mNGS"

"Clinical interpretation…**cannot be reduced to a simple yes/no readout** and requires careful integration with the patient's presentation and other diagnostic data…in a hypothesis-free testing framework, **it is the interpretation that determines whether an mNGS result advances clinical decision-making**."

— Waldrop & Reddy (Clin Infect Dis, 2026) [7]

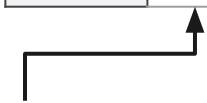
Intrathecal antimicrobials

Revisiting a topic from my first conference [link]

A **53 y/o F** with PMH including decompensated **NASH cirrhosis** (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & **hepatorenal syndrome** + **dialysis dependent** AKI p/w **abd pain, n/v, & AMS** from SNF and found to have ***Candida dubliniensis*** rhombencephalitis.

CBC	
WBC	6.1
Hgb	7.6
Platelets	**34**

Chem7	
Na	141
K	3.5
HCO3	24
BUN	12
Cr	**1.18**



- Baseline creatinine is 0.75
- When she needed dialysis, creatine $_{max}$ = 2.0

Today is "day 0" of clear CSF

- Are we really going to swing multiple weeks of AmBisome
- What is the role of IT antimicrobials?