



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



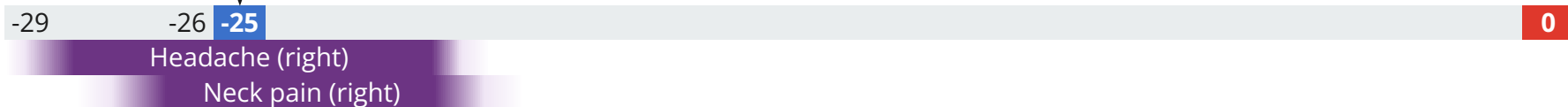
A **32 y/o F** with PMH including seasonal allergies, multiple sclerosis (on Cladribine) w/ prior right optic neuritis p/w **new intractable migraines**.

Case 1: HPI

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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

ED #1



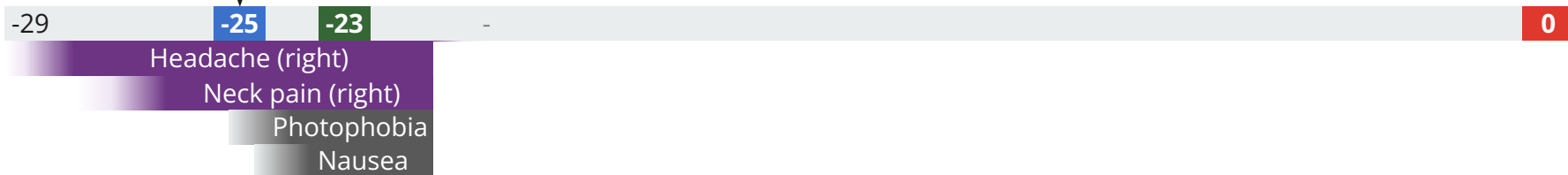
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Clinic (-23d) - Noted to have **nausea** & mild **photophobia**; left ear feels full

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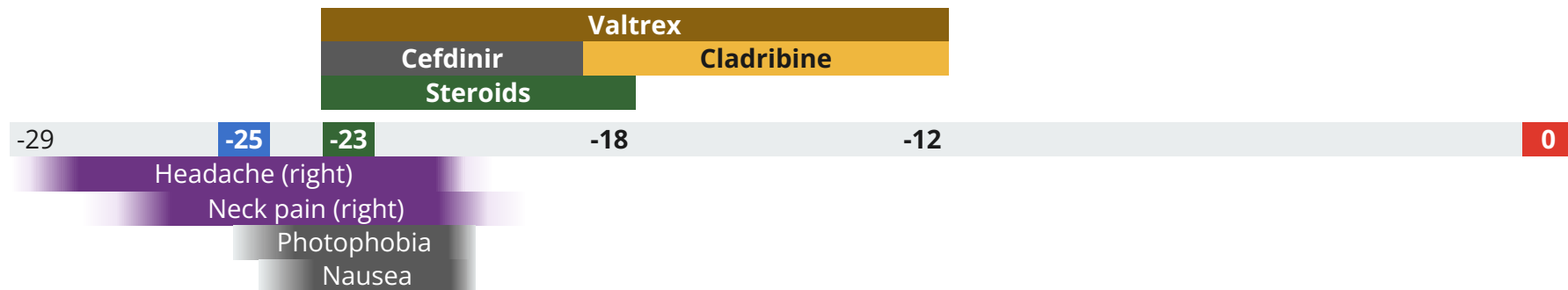
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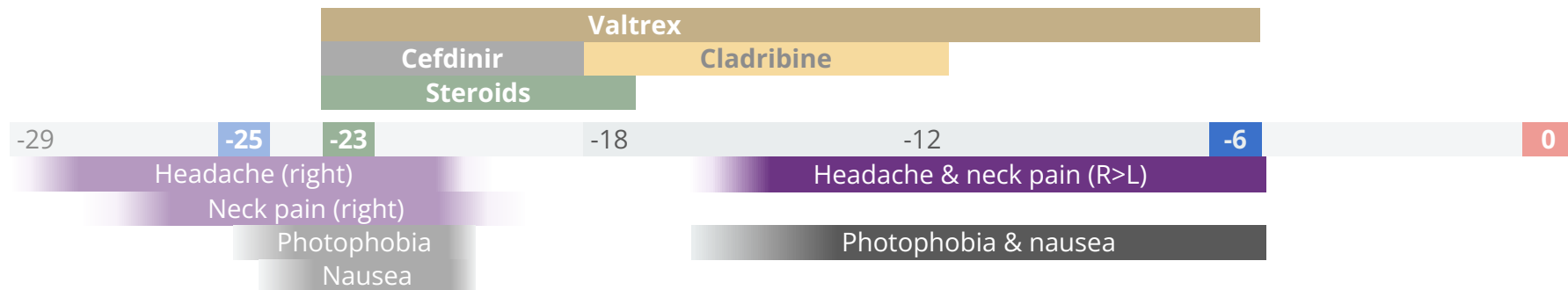
→ Pharm starts **valtrex** secondary PPx (her oral HSV tends to recur with her **Cladribine**)



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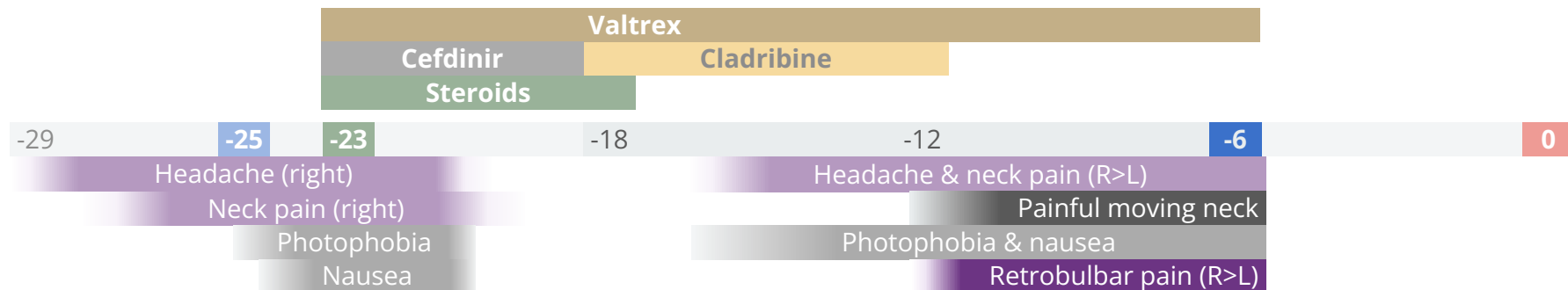
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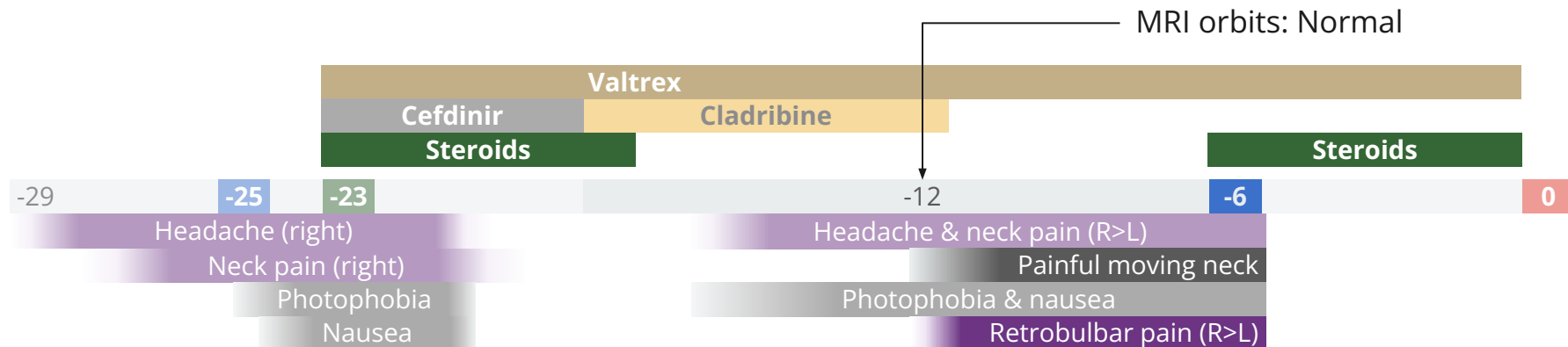
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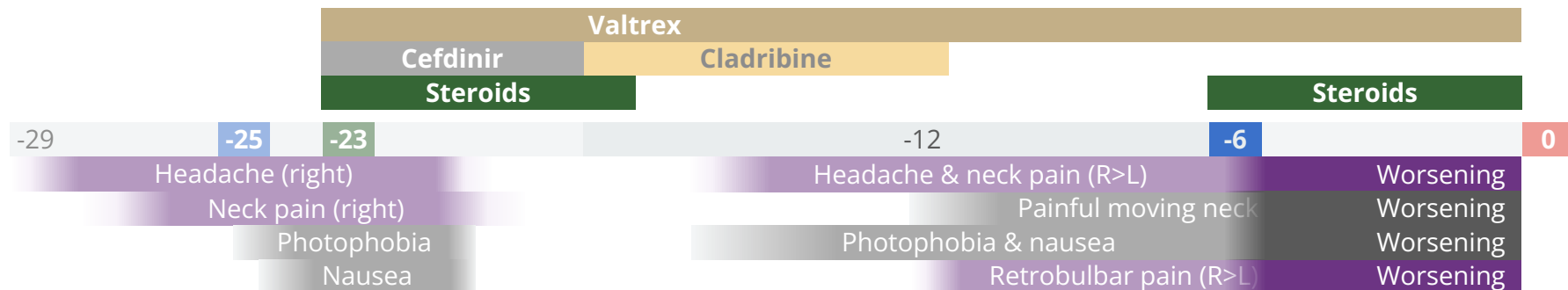


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→ This time, **she does not get better** / worsens



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

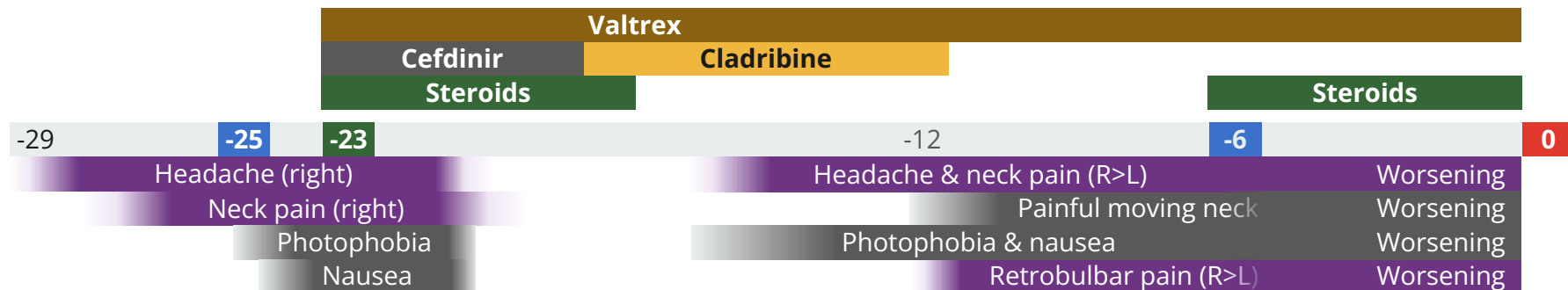
LFTs	Result
AST	11
ALT	9
Alk Phos	41
Bili	0.8
Albumin	3.3

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
Occupational	• Science educator (quite knowledgeable) • Partner works in a correctional facility, but reportedly normal TB testing
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

Serum WBC ~3.0



Case 1: Lumbar puncture

Lumbar Puncture	
Opening Pr	22 cm H2O
WBC	58
Lymph %	92
RBC	145
Protein	108
Glucose	41
Serum	94
CSF:Serum	0.44
Lactate	4.1

Serum WBC ~3.0



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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/VO



Prior MRI was just MRI of the orbits

MRI brain W/VO: 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	?

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

CSF	Result
Biofire	Negative
HSV PCR	Negative
VDRL	Negative
CryptoAg	Negative

Serum	Result
HIV	Negative
Syphilis	Negative
Lyme	?
Tick panel	?
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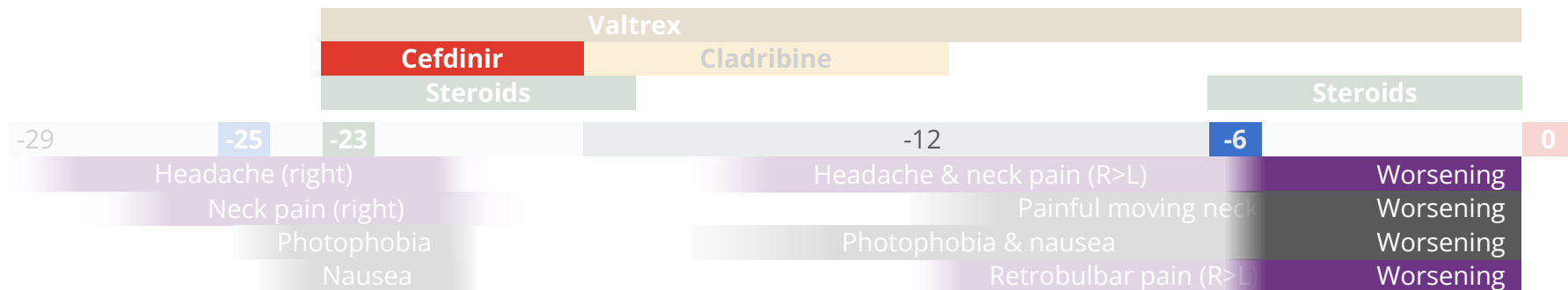
CSF	Result
Biofire	Negative
HSV PCR	Negative
VDRL	Negative
CryptoAg	Negative

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**)



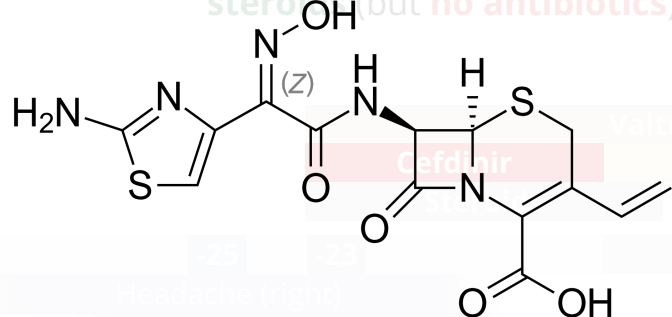
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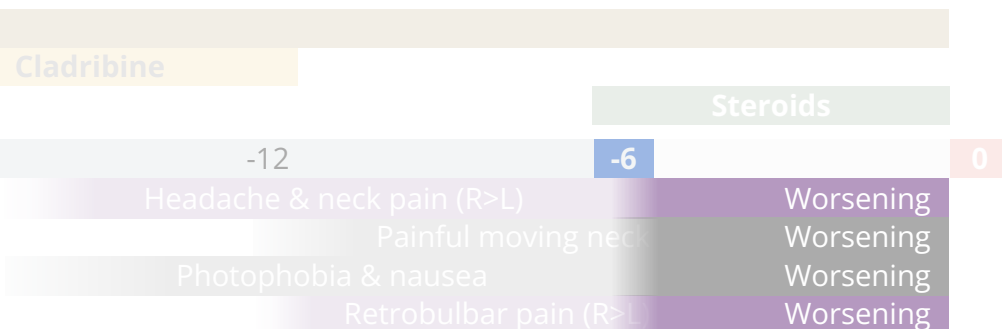
INTERVAL EVENTS / SUBJECTIVE

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**]

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



Cefdinir (looks a lot like ceftriaxone)



**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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In contrast to the:

- **second-generation** cephalosporin **cefuroxime** and
- **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



1st gen
(Keflex)



2nd gen
(cefuroxime)



3rd gen
(ceftriaxone)

Inadvertent treatment for Lyme

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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*

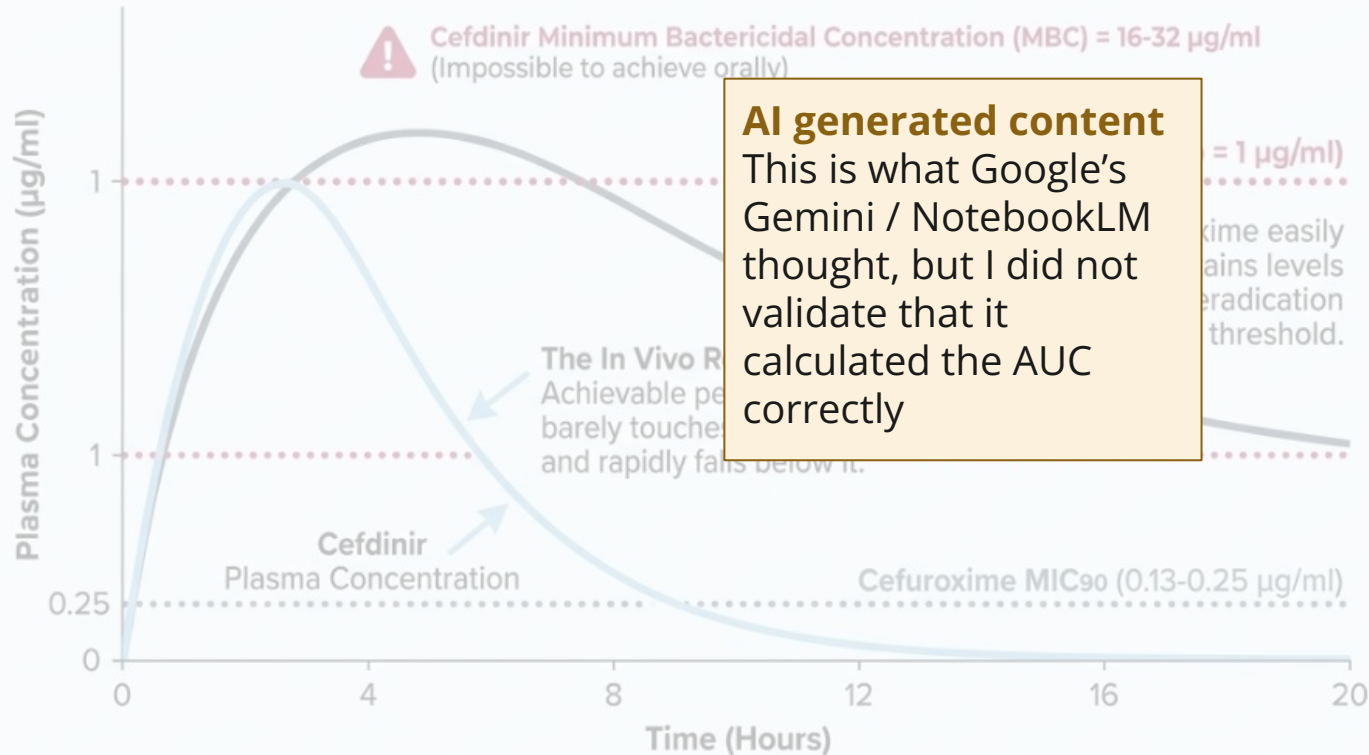
However... did not
look at bioavailability,
tissue distribution, etc

INTERVAL EVENTS / SUBJECTIVE

Says she was **feeling better** while receiving
IV antibiotic that **started with “cefe-”**

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

Cefdinir: The Gap Between Lab Susceptibility and Clinical Reality



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**



What about ~~cefepime~~ Merrem? [3]

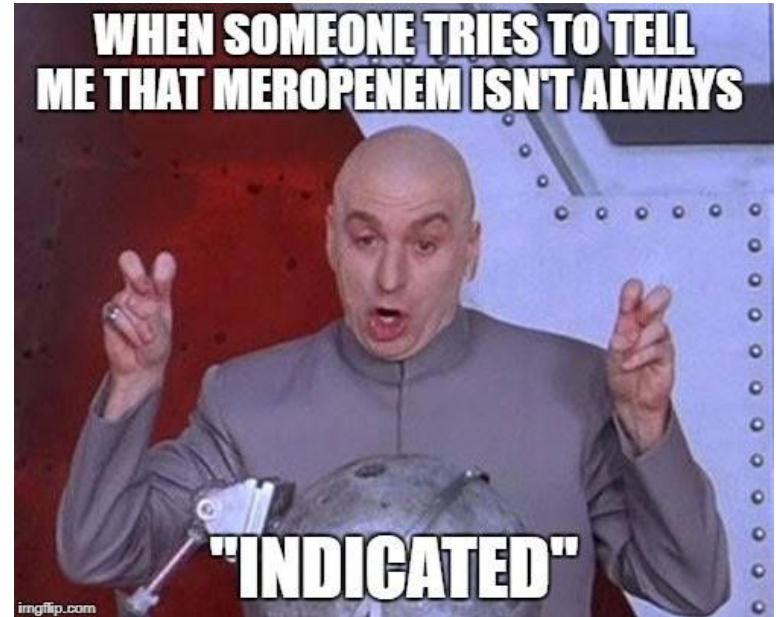
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Cefepime had activity, but **not great**

However, **meropenem** had excellent activity

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



Case #2

Case 2: HPI

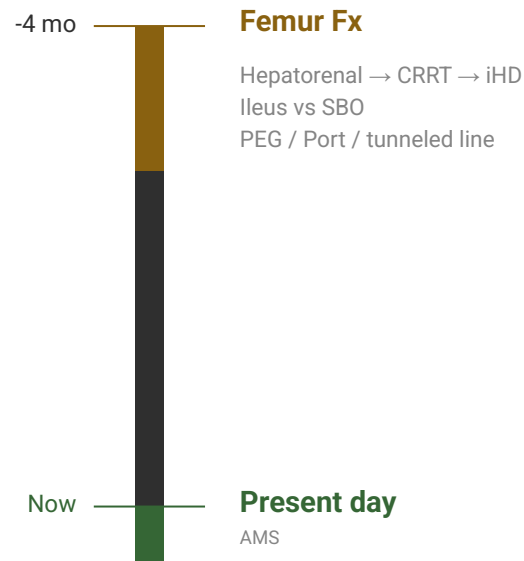


A **53 y/o F** with PMH including decompensated **NASH cirrhosis** (ascites, PSE, EV), treated HCV, prior HBV, CKD, CAD, recent admission for left femur Fx (s/p IMN 4 months ago) c/b SBO & HRS + dialysis dependent AKI p/w **GI symptoms & AMS** from SNF

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

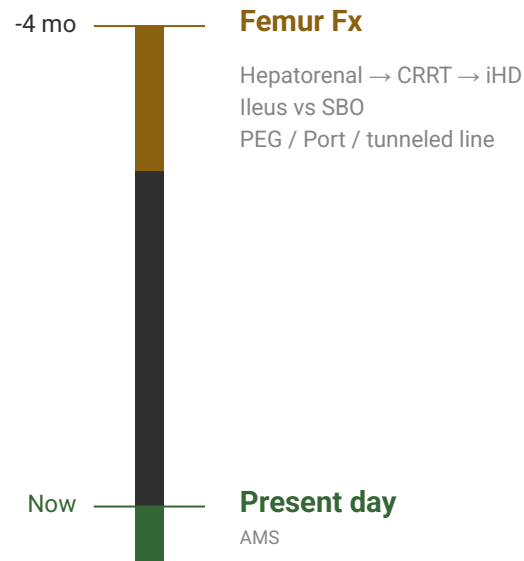
- Four months ago, slipped on some ice at home and broke left femur
 - Uneventful ORIF
- Then had AKI → needed dialysis CVC for possible iHD
 - Ileus vs possible SBO
- During line placement, had emesis & aspiration → intubated and sent to MICU
 - Started on CRRT



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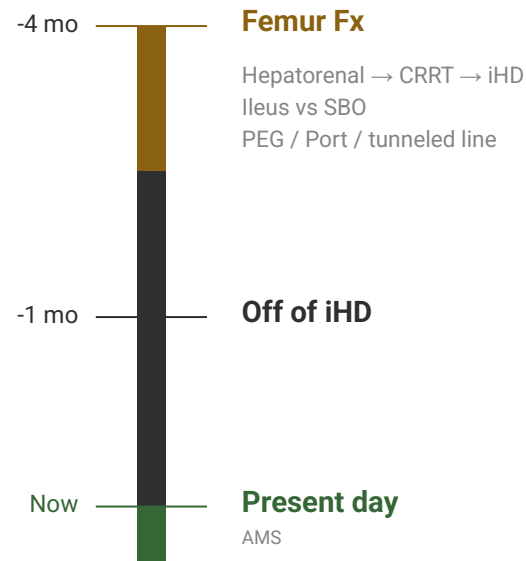
- SBO: Failed swallow studies → got PEG
- Nutrition: was on TPN → port placed (for TPN)
- AKI/HRS: CRRT → iHD
 - Temp CVC removed → tunneled line placed
- Hepatology stuff: Delisted due to prolonged intubation
 - CT showed new splenic thrombosis (post-op)
- ID stuff: Not really much, treated for aspiration



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

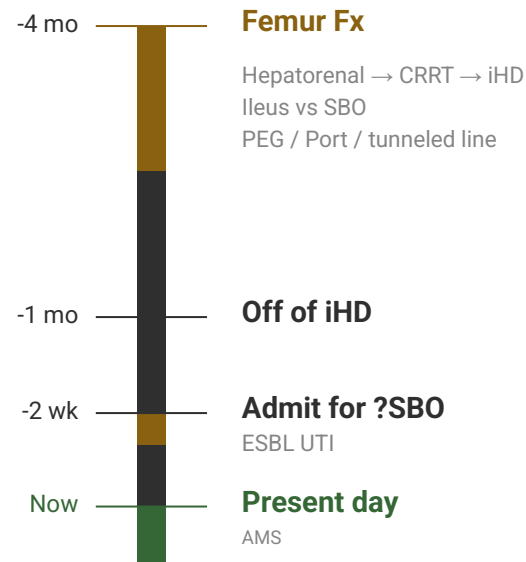


Case 2: HPI - since last hospital stay

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

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)



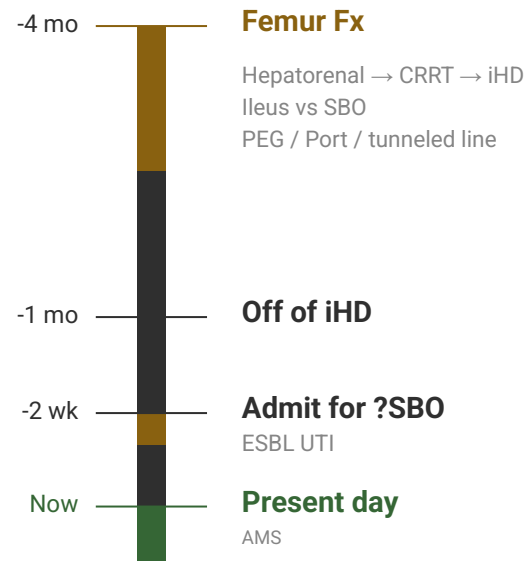
Case 2: HPI - Present admission

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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	Unable to obtain
Occupational	
Substance & needles	
Animals	
Exposures	

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

LFTs	Result
AST	18
ALT	14
Alk Phos	111
Bili	3.5

More or less
baseline

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

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

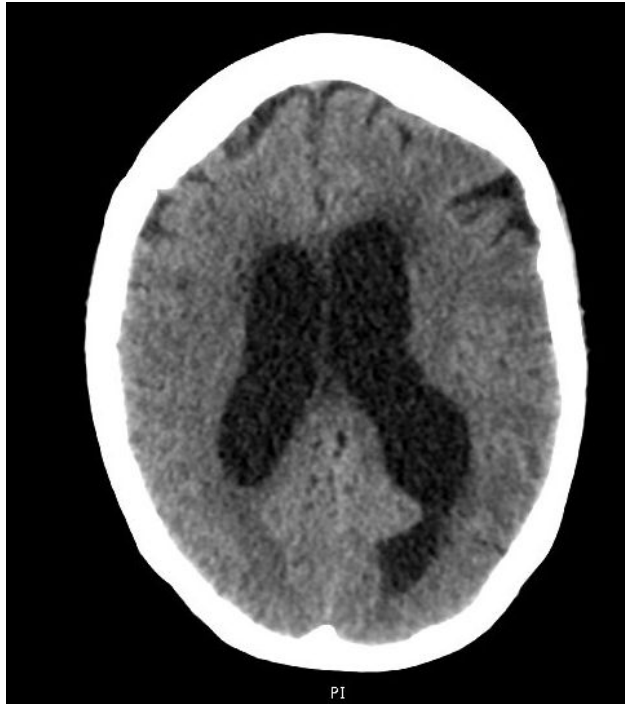
Possible ileus

- 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

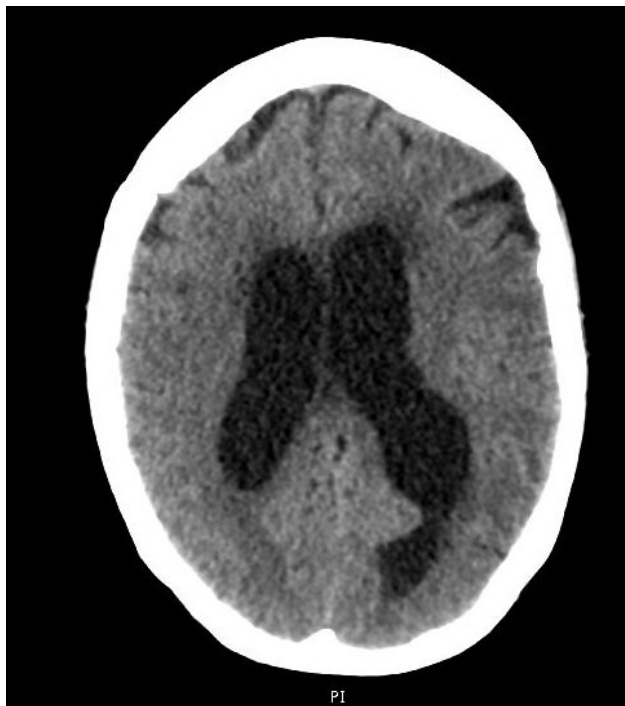


Current admission



Femur fracture admission

Case 2: CT head



Current admission

CT head WO

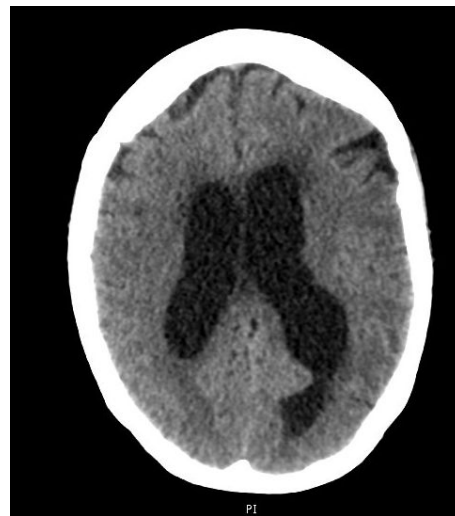
New onset hydrocephalus pattern with probable **subependymal edema** in the periventricular region.

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**



Current admission



Femur fracture admission

CBC	
WBC	16.2
Hgb	11.4
Platelets	141
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Lymph #	700
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Chem7	
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LFTs	
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Case 2: Ruby transfer

- Admitted to NCCU
- Overnight IRRFlow 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

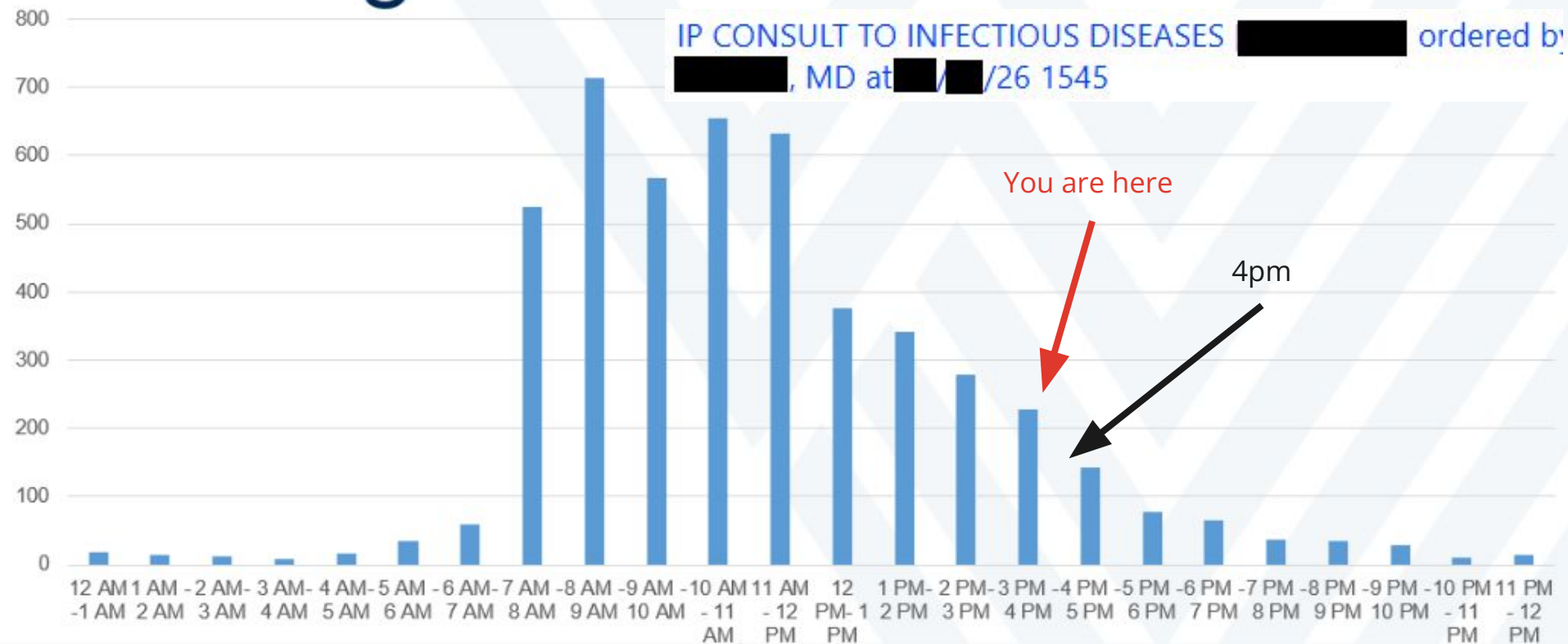
“Initial pressure was low”



Serum	Result
HIV	Negative
HCV PCR	TND

Timing of ID Consult Order

IP CONSULT TO INFECTIOUS DISEASES [REDACTED] ordered by [REDACTED], MD at [REDACTED]/[REDACTED]/26 1545



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	???

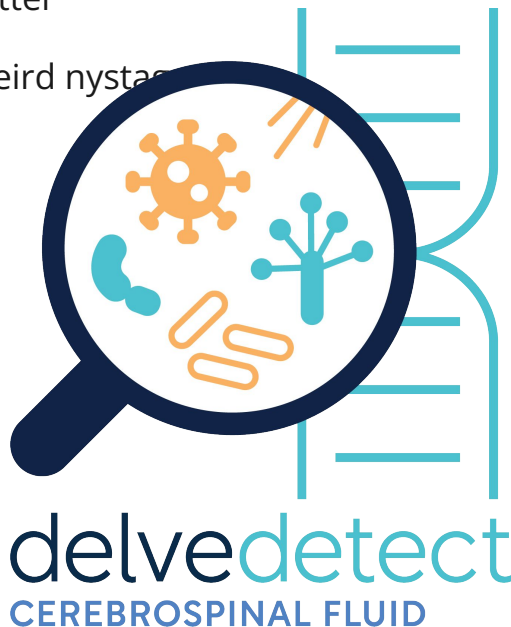
Case 2: The next 48 hours

Remains afebrile (but cirrhosis)

Mental status not better

Starts getting very weird nystagmus

Next steps?

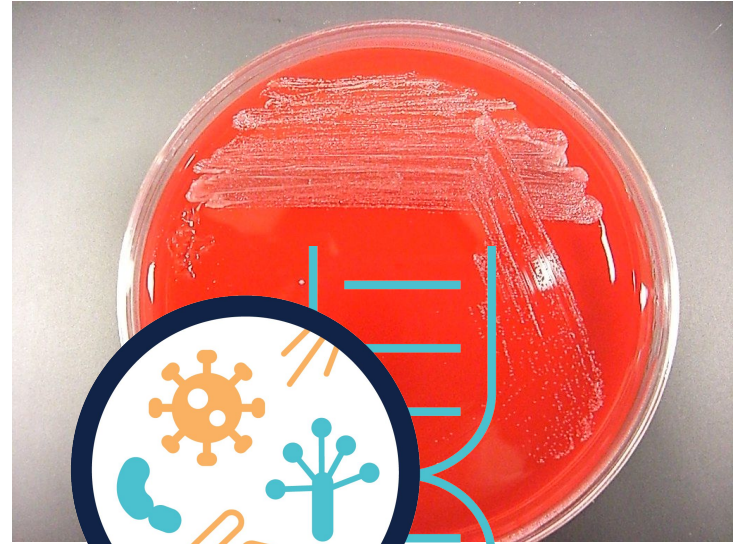


CSF	Day 1	Day 3
EVD mode	Drain only	Irrigation
WBC	86	160
Neut %	75%	83%
RBC	367	13
Protein	145	18
Glucose	56	32
Routine Cx	NG@2D	G/S neg
Fungal Cx	NG@2D	...
AFB Cx	Smear (-)	...

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



delvedetect
CEREBROSPINAL FLUID

Case 2: The results

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

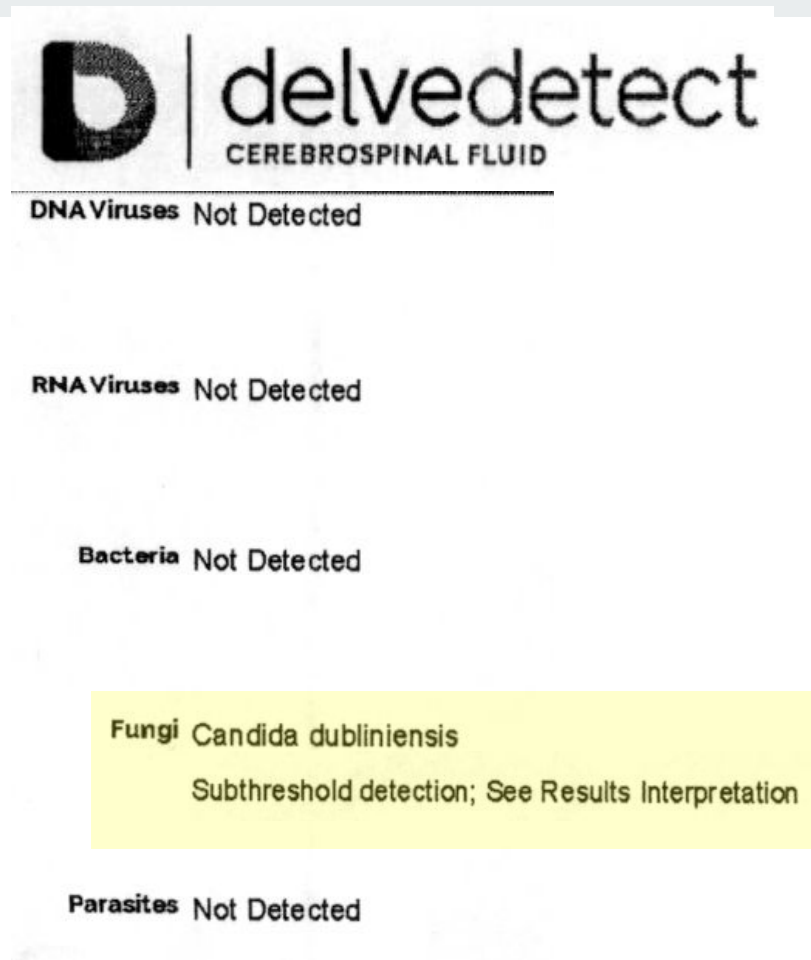
- 5-FC: 0.06 (S)
- Flucon: 0.50 (S)

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.

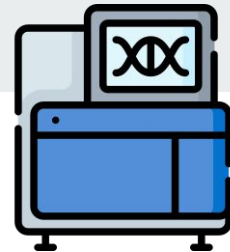
SPECIMEN NOTES

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



mNGS

—



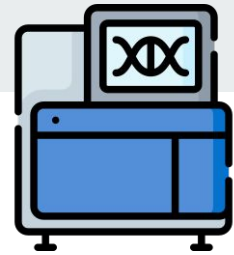
Alphabet soup of molecular testing [7]

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

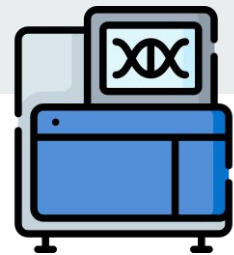
Traditional PCR

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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C Protocol for Metagenomic NGS Assay

Clinical Laboratory Sequencing

Receive sample

Isolate DNA and RNA

Construct metagenomic NGS library

Generate sequence data

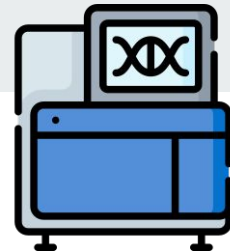
SURPI+ Computational Analysis

Filter for high-quality sequences

Subtract human background sequences

Detect pathogens

Report results in EMR



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: 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**

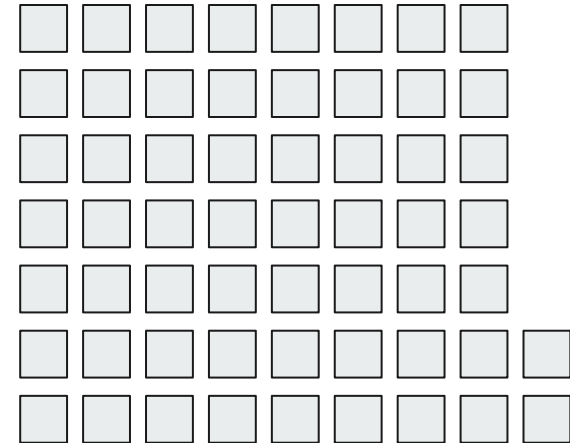
- e.g. 2014 case where a teenager had **30+ conventional tests**, only for mNGS to diagnosed neuro-leptospirosis [7]



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



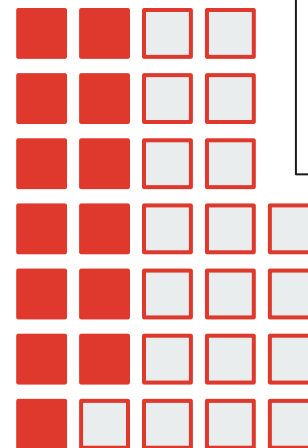
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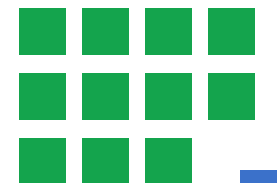
204 patients, **58 CNS infections**

- **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

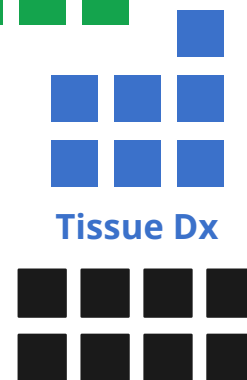
Dx on mNGS



Serologic Dx



Tissue Dx



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)

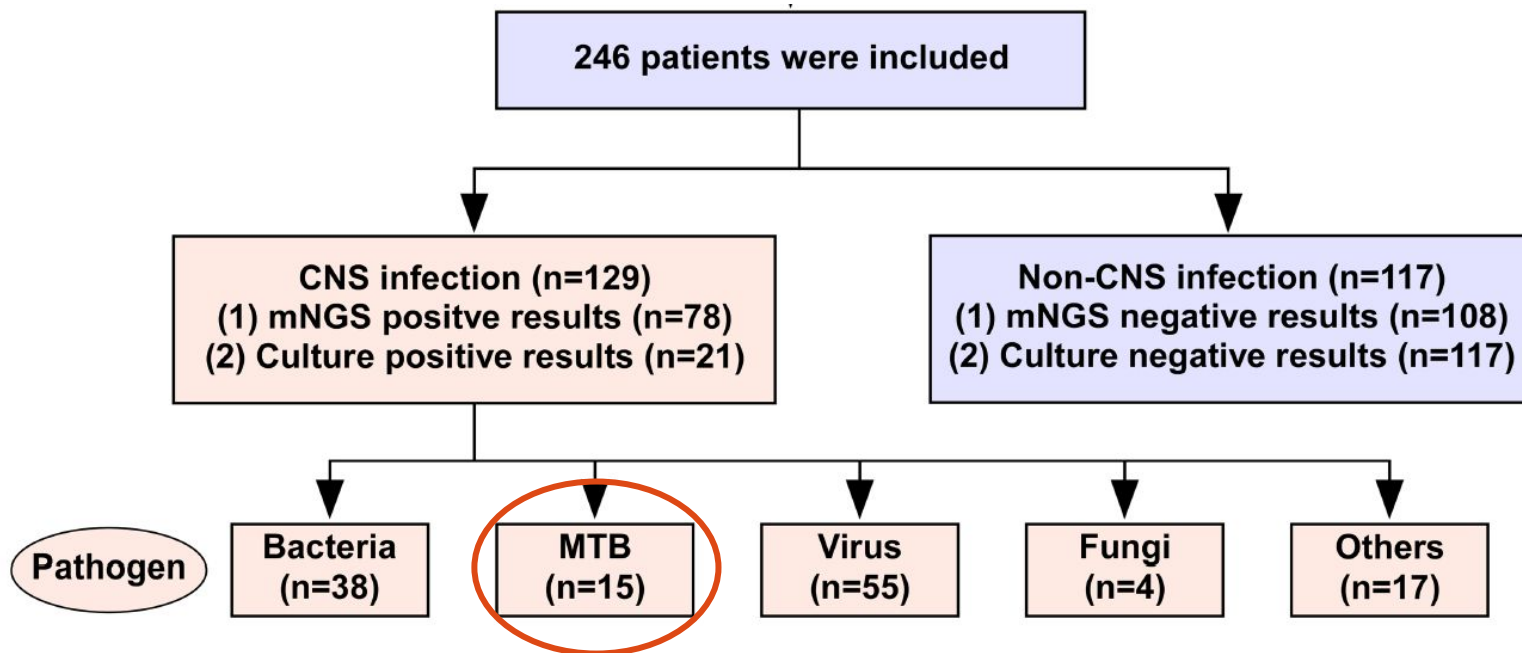
Defining “definitive diagnosis”

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]

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]

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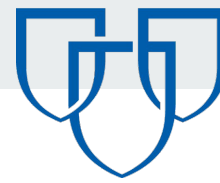
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Cut for time [6]

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%

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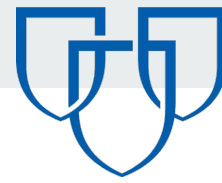


Mayo clinic review [8]

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)	



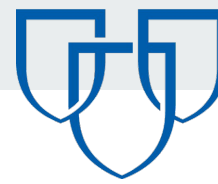
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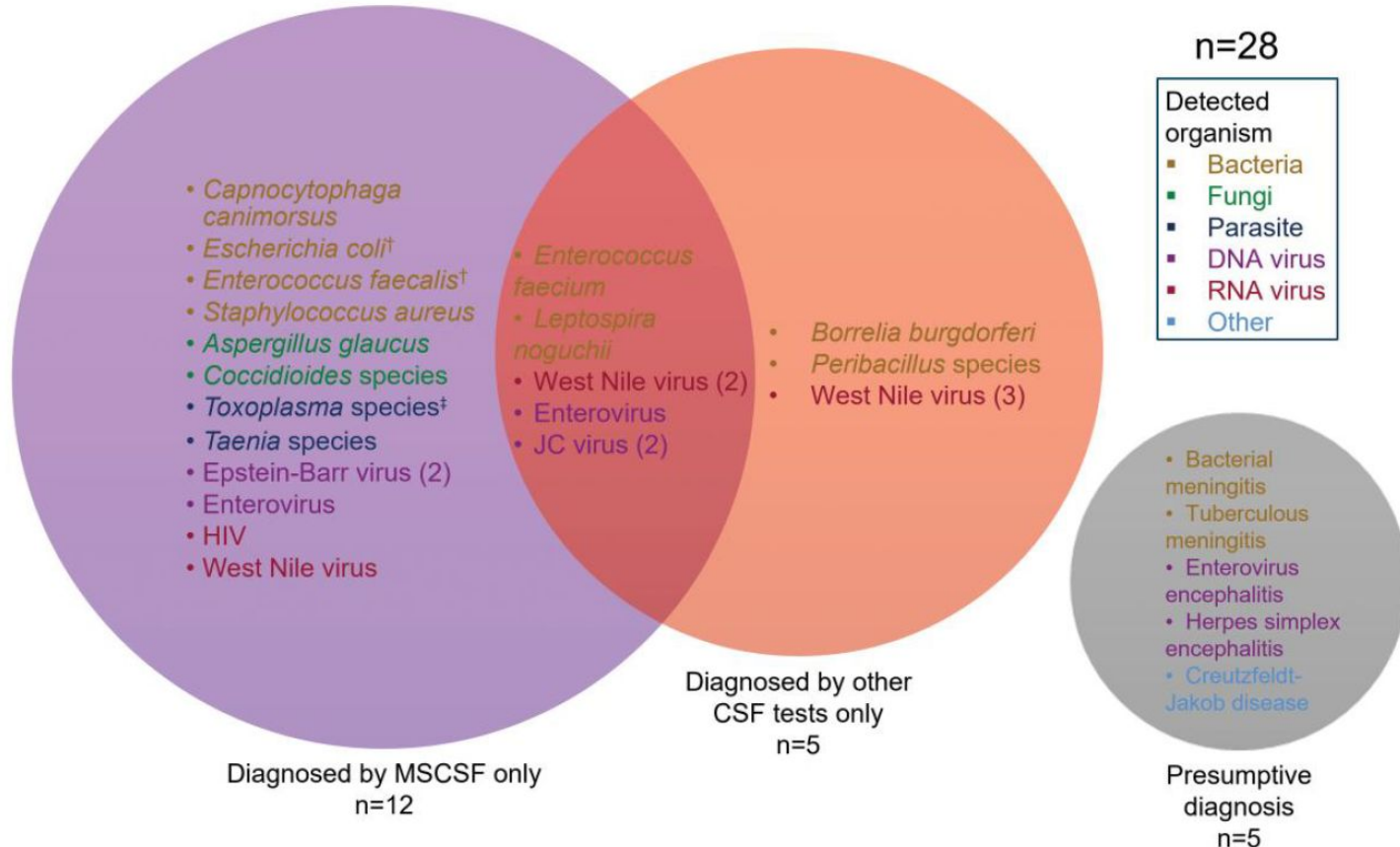
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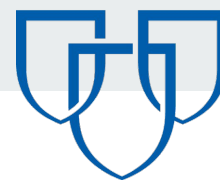
Odds of positive test

- 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?

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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

Limitations with mNGS [7]



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- 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 not 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.

Today is “day 0” of clear CSF

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

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