# Hidden Infections: The Organisms You Might Not See (Initially)

# AGENDA

- 3 Case Studies
  - Clinical Presentation
  - Potential dx
  - Detection Methods
  - Outcomes

# OBJECTIVES

- Identify risk factors and pathogens that may cause meningoencephalopthy in previously healthy teenager.
- Differentiate potential infectious agents that are associated with sever rhabdomyolysis.
- Analyze laboratory data and clinical history to postulate a source of infection in a hospitalized patient with complicated presentation.

# CASE 1

Summertime Sickness

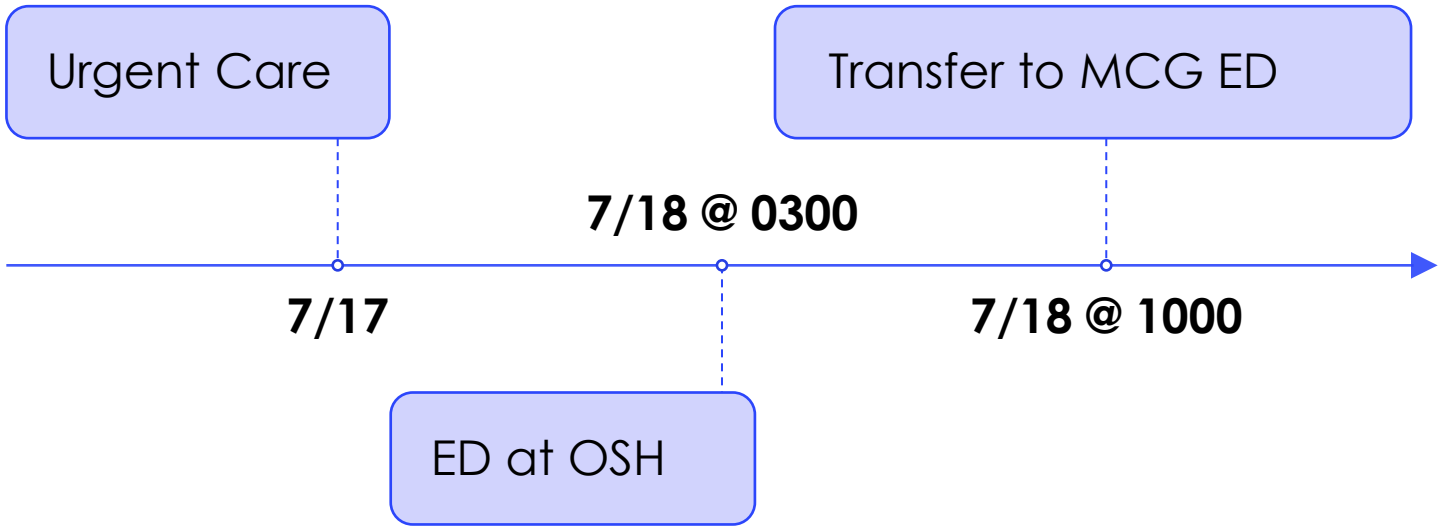
# CASE #1

- 17 yoF
- CC: headache, fever, sore neck for several days not resolved with Tylenol/Motrin
- Urgent Care: sinusitis dx given abx

# PROGRESSION

- HA & fever persisted
- Ataxia, flexor posturing
- Increasingly altered
- DDx – Meningitis, Encephalitis
- Unsuccessful LP
- Intubated
- Admitted to PICU

**Clinical Timeline**



# PICU ADMISSION

H&P

- WBC = 21k, Segs = 96%
- Fever = 104F
- ICPs = 40-50 (5-15 mmHg)
- MRI = hydrocephalus, leptomeningitis, and encephalitis, cortical infarct

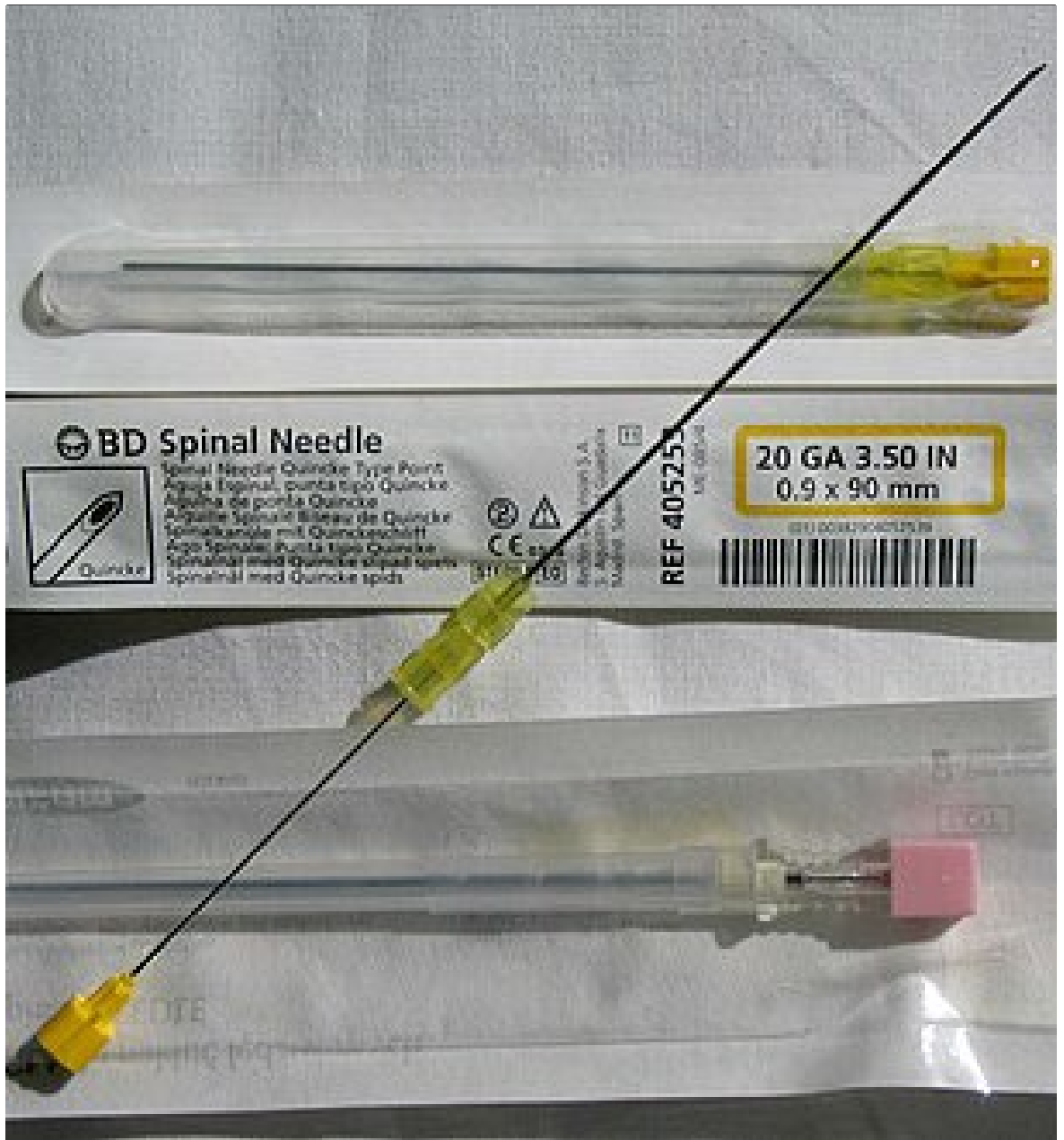
Warranted ID Consult →

Exposure

- Residence near woods with 3 acres of land.
- 7 cats and a dog; all are indoor/outdoor pets.
- Mother reported tick removal from pt's arm the previous week.
- No exposure to horses, cows, reptiles, or exotic pets.
- Recent swimming in a nearby lake.

# ID RECS

- Lumbar Puncture
  - send for cell count, glucose, chemistry, culture and gram stain and HSV as well as enterovirus PCR.
  - Hold a tube to be sent for an ME panel
  - Hold a tube with consideration for acanthamoeba PCR if all CSF testing is unrevealing due to lake exposure with severe meningoencephalitis.
  - Please put this patient on isolation until we rule out Neisseria meningitidis.



# CSF RESULTS

- EVD placed @ 1700 7/18
- CSF not draining
- Small amount (3-4 mLs) CSF appear moderately purulent but not sent to lab
- Repeat LP on 7/19

# PROGRESSION

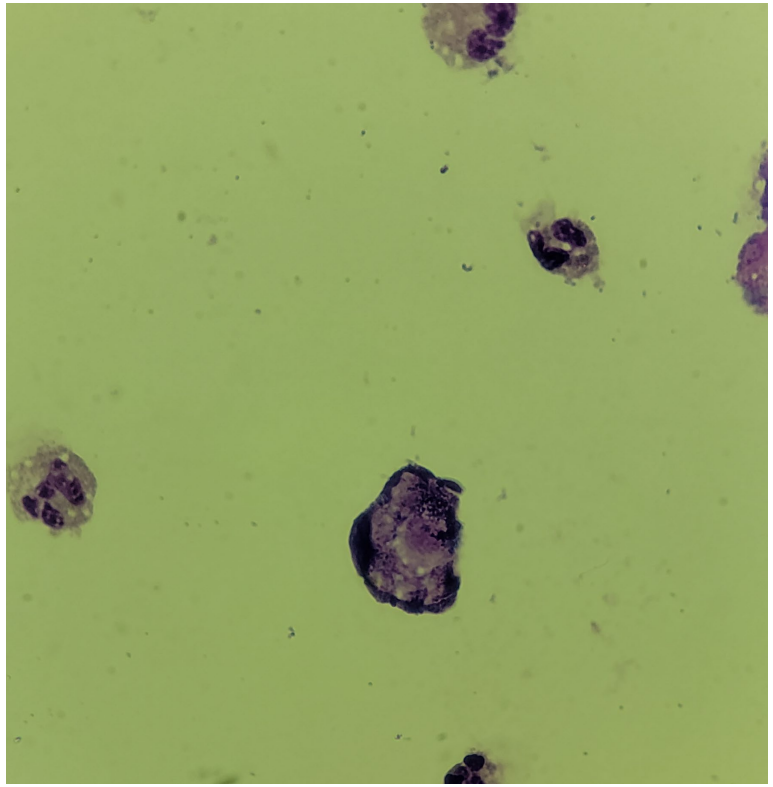
## 7/19

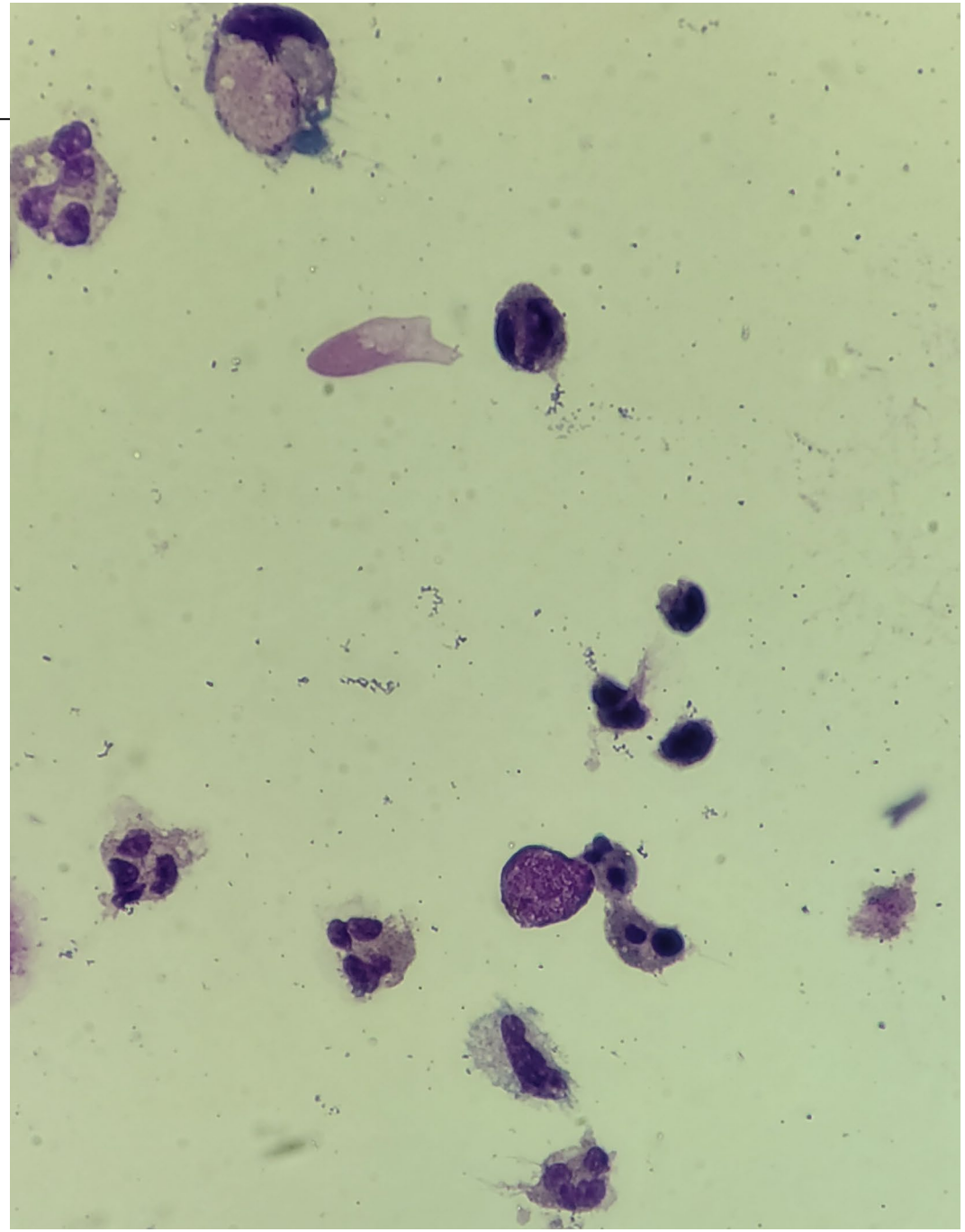
- Bilateral pulmonary infiltrates with pulmonary edema and ARF
- Severely diminished systolic function
- Electrolyte derangements
- Hyperosmolar

## 7/20*

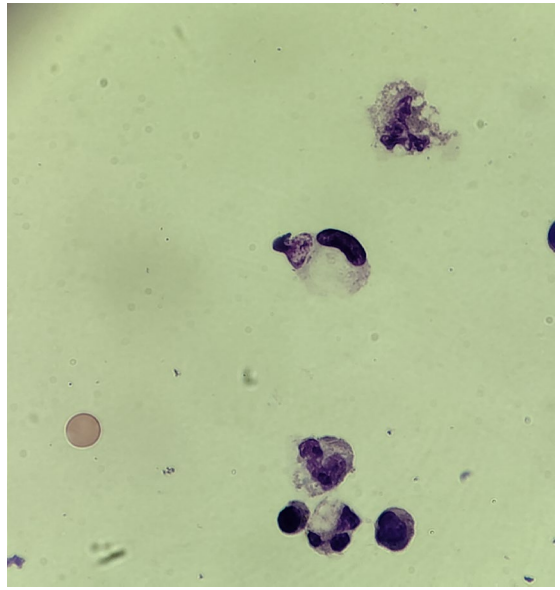
- Brain herniation concern for HIE
- Send Outs Received Sample***

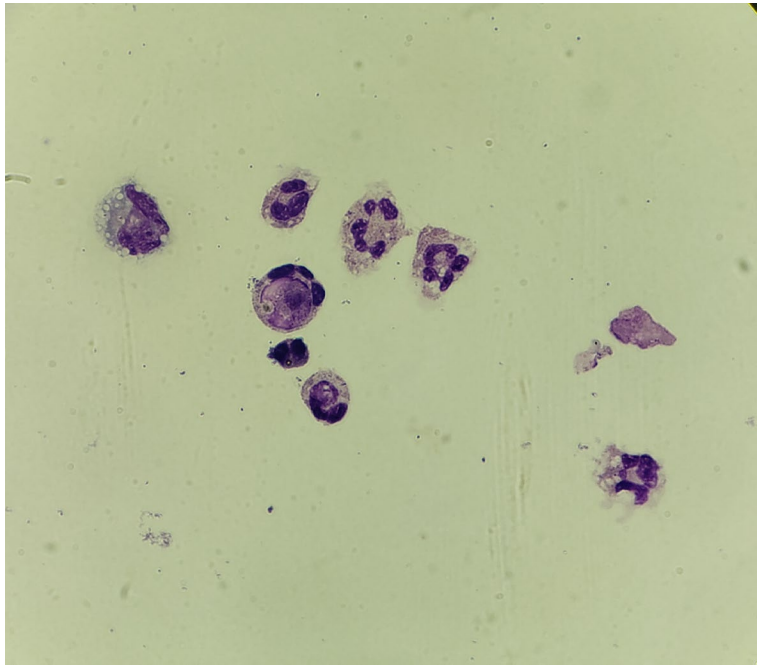
# CSF SLIDES

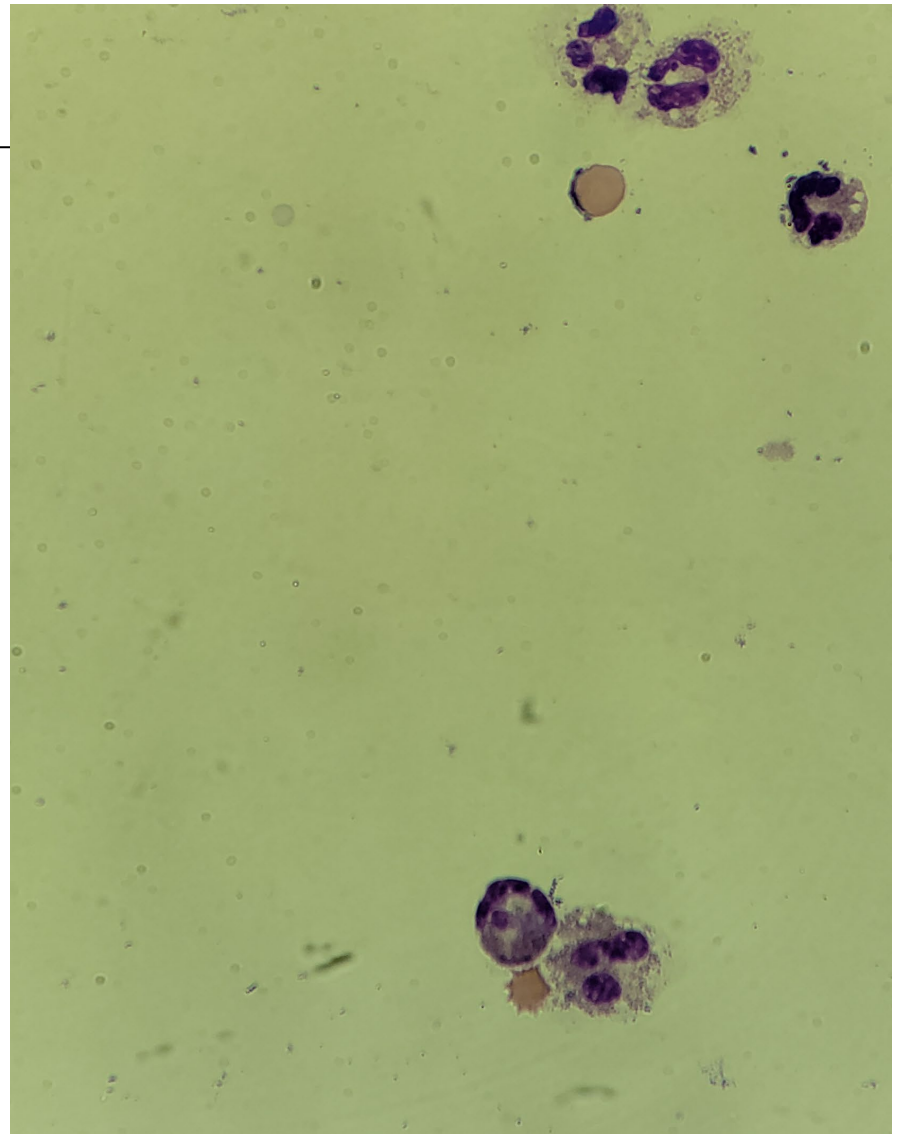




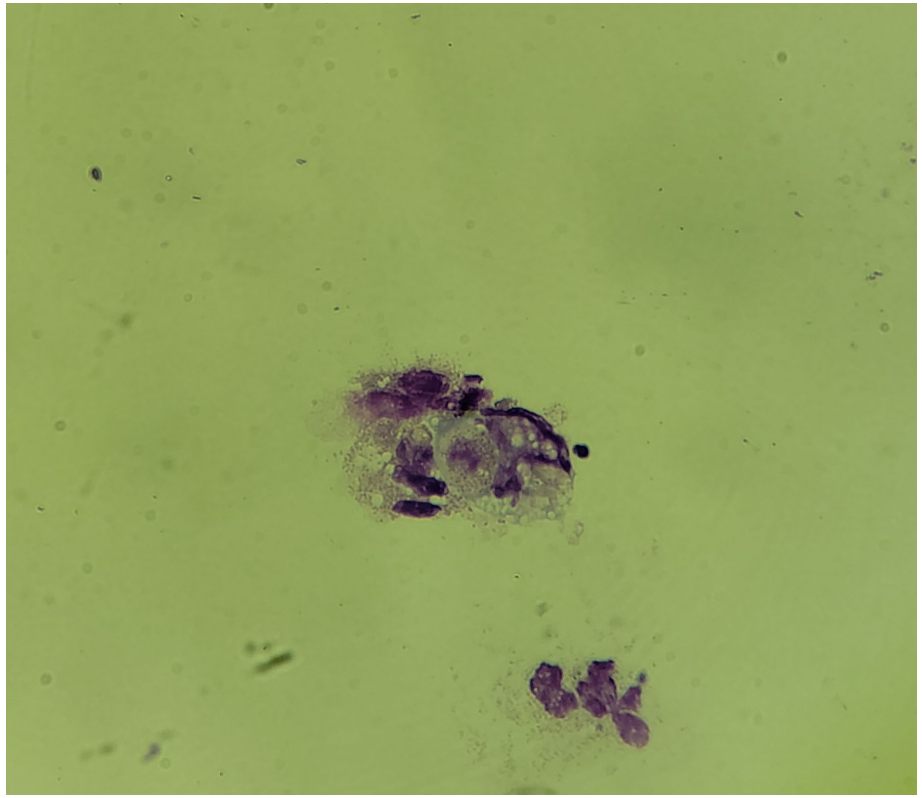
# CSF SLIDES

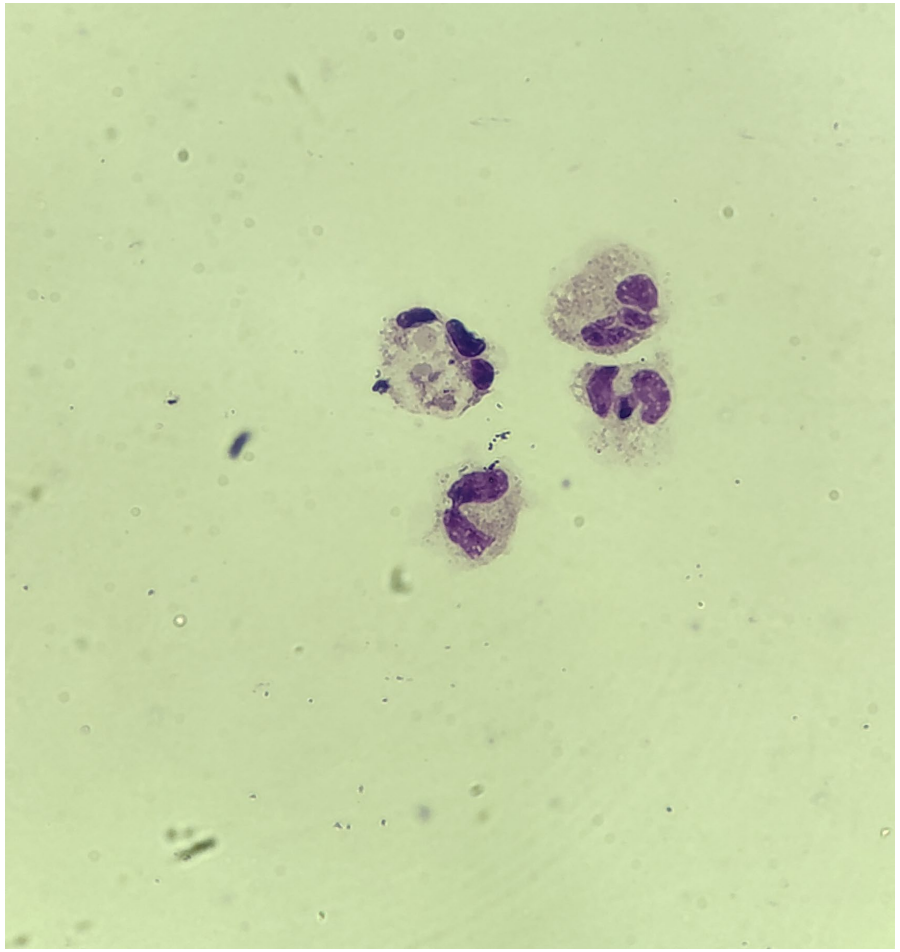






# CSF SLIDES





# AMEBAE PCR RESULTS

**1.) (Medium Importance) Result Comment by Contributor_system, MAYO REF LAB on July 23, 2023 00:33 EDT**

| Test | Result | Flag | Unit | RefValue |
|---|---|---|---|---|
| Free-living Amebae Detection, PCR | | | | |
| Specimen Source | CSF | | | |
| Acanthamoeba species PCR | Negative | | | Negative |
| Naegleria fowleri PCR | Positive | C | | Negative |

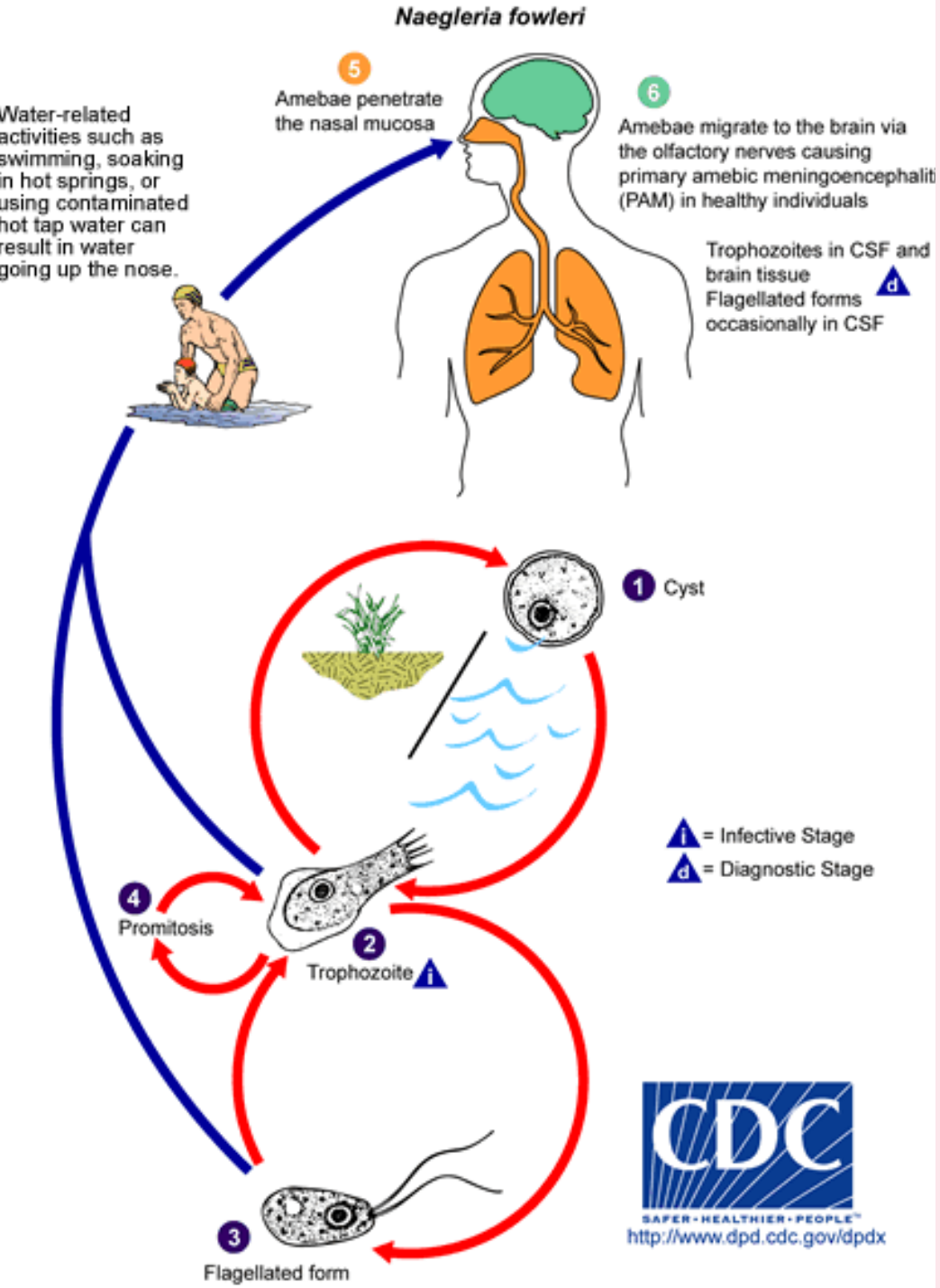
Critical result.

----------ADDITIONAL INFORMATION----------

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

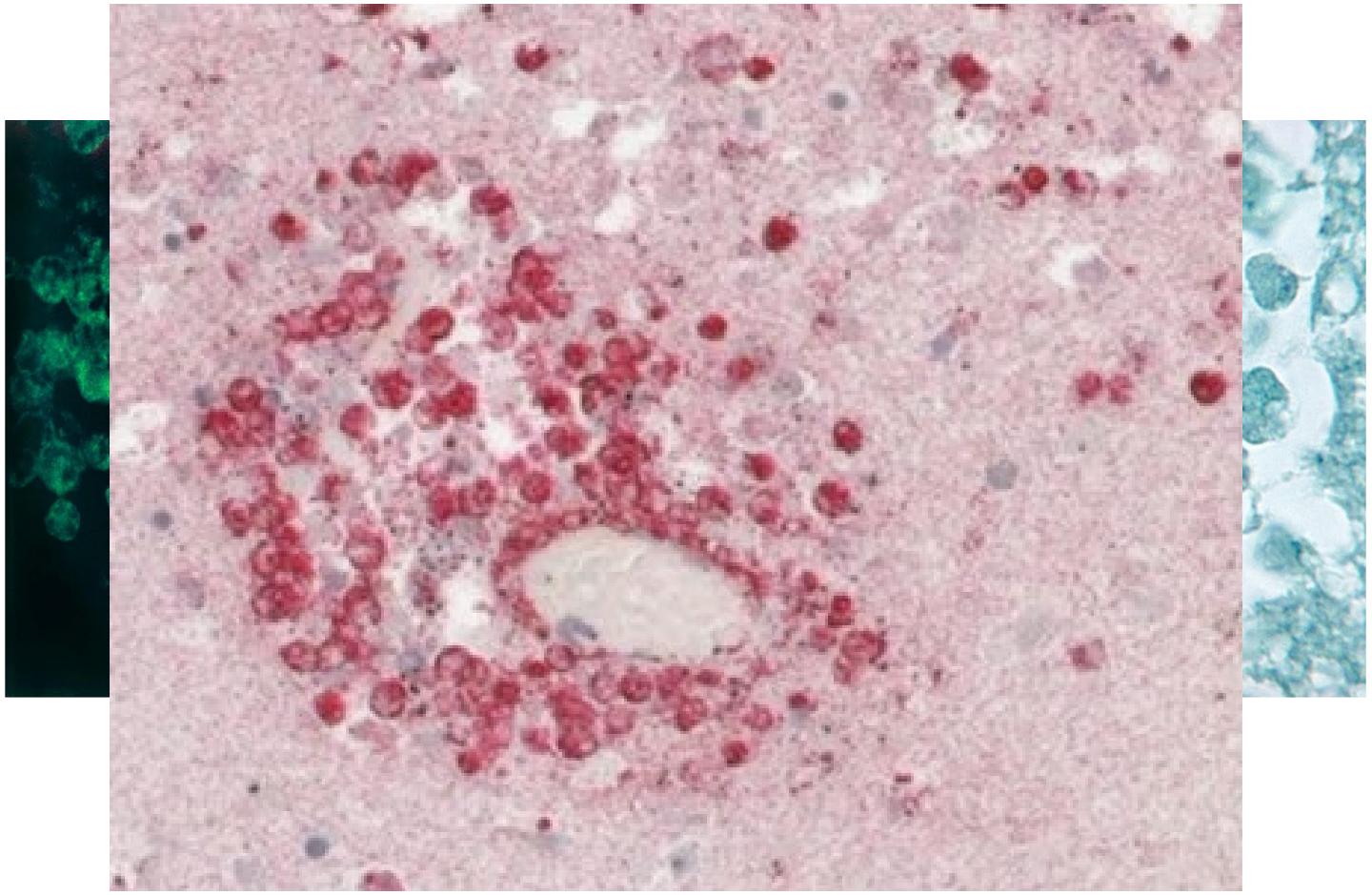
| | | | | |
|---|---|---|---|---|
| Balamuthia mandrillaris PCR | Negative | | | Negative |

Test Performed by:
Mayo Clinic Laboratories - Rochester Main Campus
200 First Street SW, Rochester, MN 55905
Lab Director: William G. Morice M.D. Ph.D.; CLIA# 24D0404292




# PRIMARY AMEBIC MENINGOENCEPHALITIS (PAM)

# DETECTION METHODS



- PCR on CSF or brain tissue
- IHC testing and IIF staining that use specific antibodies against *Naegleria fowleri* to detect the ameba
- Direct visualization by examining CSF under a microscope.

# OUTCOMES

- MRI detected brain herniation 7/20
- Brain death exam ordered after 24hrs off sedation
- Expired 7/21

# QUESTIONS ON THIS CASE?

# CASE 2

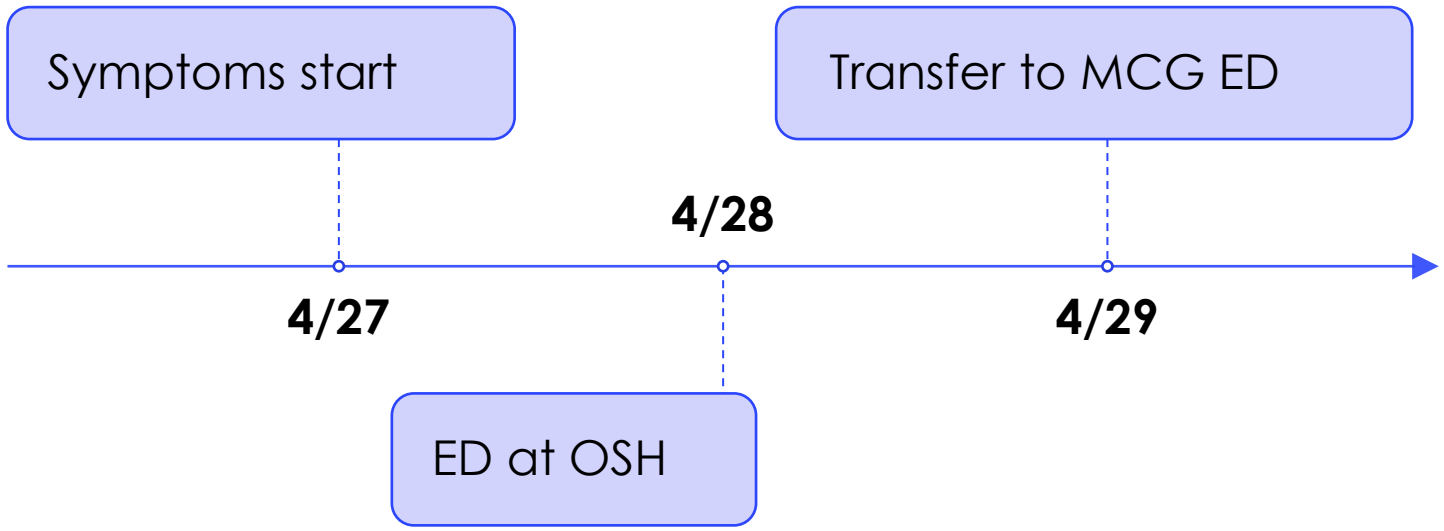
Tired Truckdriver

# CASE #2

- 27 yoM
- CC: diarrhea, dehydration, light headedness, BL LE weakness
- OSH: tachycardic (HR 130s-140s), febrile (102F), left lobe PNA
  - Labs: WBC 20, LA 2.1, D-dimer 3.186, hsTNI 106, Creat 5.4, NA 133

# INITIAL WORKUP

## Clinical Timeline




- BUN = 41 mg/dL
- CREA = 5.4 mg/dL
- AST = 688 U/L
- ALT = 179 U/L
- CK = 161763 U/L
- TnI = 0.14 ng/nL

# INTERNAL MEDICINE ADMISSION

H&P

- Truck driver
- Obese
- No PMH
- Family hx of “heart issues”

DDX

- Sepsis CAP
- Food poisoning vs gastroenteritis
- Troponinemia
- Concern for PE
- AKI
- Rhabdomyolysis
- Transaminitis

# PROGRESSION

## 4/29

- AKI → ARF
- Metabolic Acidosis
- Hemodialysis initiated
- Transferred to MICU

## 4/30

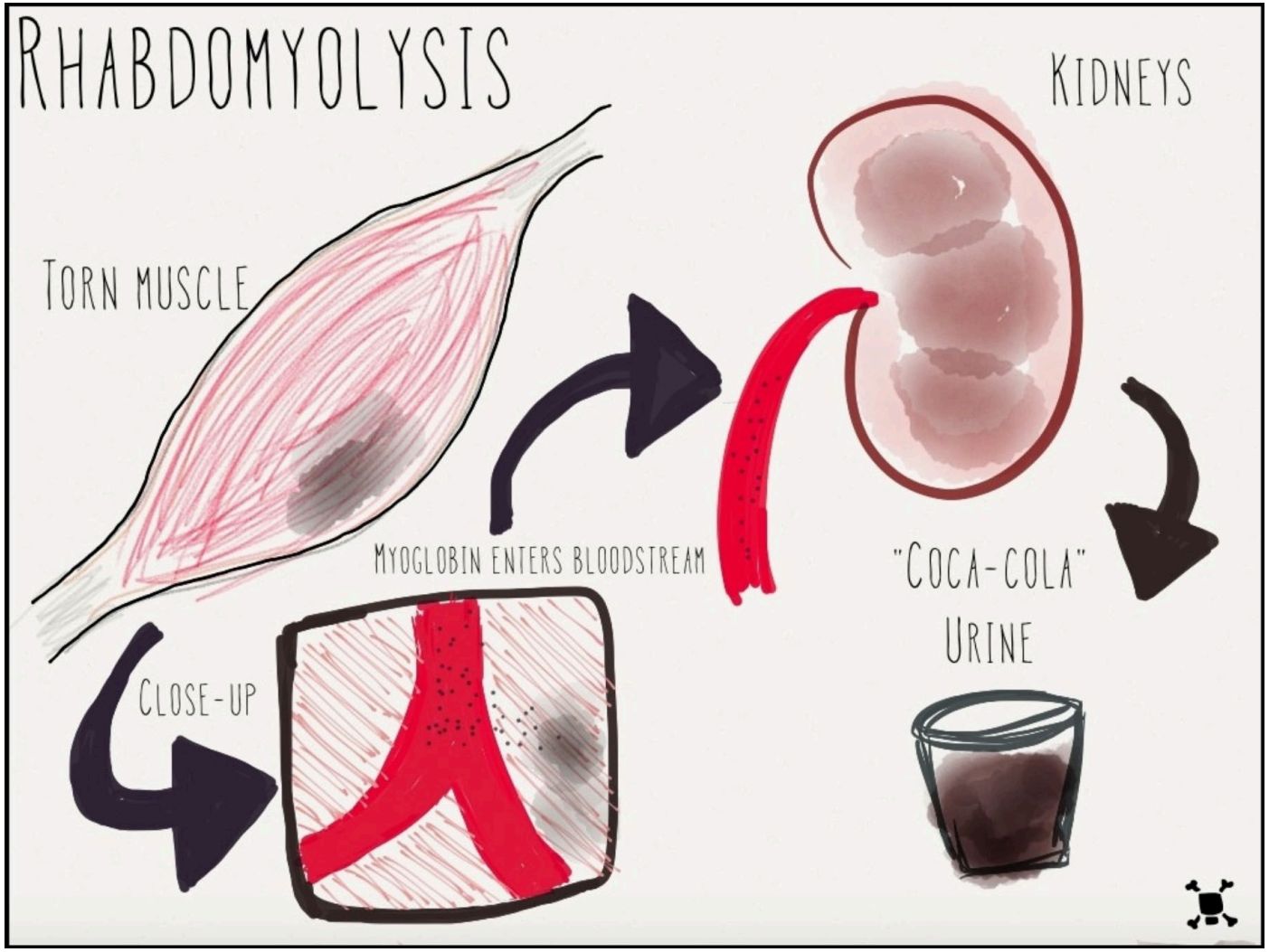
- Work up for autoimmune and tick-borne illness
- Uric Acid 17.5 mg/dL (H)
- Phos 12.8 mg/dL (!)
- Transaminitis worsening
- Stool and BCx pending
- PE ruled out
- CK = 427,466 (H) U/L

## 5/1

- CK = 791,464 (H) U/L
- Dark tea colored urine

# RHEUMATOLOGY (5/2)

- Injury to muscles with unclear etiology
- Acute onset of symptoms in a previously healthy individual leans toward an infectious etiology such as a viral myositis/Pyomyositis.
  - high WBC & fevers
- Labs:
  - anti-CN1, anti-HMGCR, aldolase, dsDNA, and anti-smith to complete the collection of Myositis Specific antibodies



# INFECTIOUS DISEASE (5/3)

- Domestic US travel with recent trip to NY
- No animal exposure
- No changes in diet
- No sick contacts
- Monagmous relationship
- Labs:
  - RPP
  - PCR viral load or virus specific antibodies if high suspicion for viral myositis (Adenovirus, Coxsackievirus, EBV, etc.)

***CRRT initiated***

# LAB WORKUP

- Autoimmune:
  - ANA = neg
  - Hepatitis = neg
  - Myositis Panel = neg
  - Tickborne illness panel = neg
  - Stool and BCx = neg
  - RPP →

| Microbiology | |
|---|---|
| Blood Culture Site 1 | |
| Blood Culture Site 2 | |
| Cul Stool Rout | |
| Adenovirus PCR | * Not Detected |
| Coronavirus 22 | * Not Detected |
| Coronavirus HK | * Not Detected |
| Coronavirus NL | * Not Detected |
| Coronavirus OC | * Not Detected |
| Influenza A | * Not Detected |
| Influenza A-H1 | * Not Applicable |
| Influenza A-H3 | * Not Applicable |
| Influenza A2009 | * Not Applicable |
| Influenza B | * Not Detected |
| Mpneumovirus | * Not Detected |
| Parainfluenza Virus 1 | * Not Detected |
| Parainfluenza Virus 2 | * Not Detected |
| Parainfluenza Virus 3 | * Not Detected |
| Parainfluenza Virus 4 | * Not Detected |
| Resp Sync Virus | * Not Detected |
| Bordetella pertusis | * Not Detected |
| Rhinovirus/Enterovirus | * Not Detected |
| Chlampneumoniae | * Not Detected |
| Mycopneumoniae | * Not Detected |
| Shiga Toxin | |
| Bordetella parapertussis | Not Detected |
| Coronavirus 2 (SARS-CoV-2) | Not Detected |

# LAB WORKUP

- Virus Specific:
  - Adenovirus PCR = Not detected
  - EBV = positive for past infection
  - Coxsackie A and B Abs →

| Lab Results | 5/3/2024 12:22 EDT |
|---|---|
| **Serology** | |
| CMV-IGG | * Negative |
| CMV IGM | * Negative |
| CoxA Ab Type10 REF | <1:8 |
| CoxA Ab Type16 REF | * <1:8 |
| CoxA Ab Type2 REF | <1:8 |
| CoxA Ab Type4 REF | <1:8 |
| CoxA Ab Type7 REF | <1:8 |
| CoxA Ab Type9 REF | <1:8 |
| CoxB Ab Type1 REF | 1:20 |
| CoxB Ab Type2 REF | 1:20 |
| CoxB Ab Type3 REF | A 1:160 |
| CoxB Ab Type4 REF | 1:40 |
| CoxB Ab Type5 REF | <1:10 |
| CoxB Ab Type6 REF | * <1:10 |

# METHODS OF DETECTION

**Reverse Transcription Polymerase Chain Reaction (RT-PCR)**

- **Advantages**: High sensitivity and specificity; rapid results.
- **Limitations**: May not identify specific serotypes without additional typing methods.

**Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP)**

- **Advantages**: Does not require sophisticated equipment; suitable for resource-limited settings.
- **Limitations**: Still under evaluation for widespread clinical use.

**Viral Culture**

- **Advantages**: Allows for serotyping of the virus.
- **Limitations**: Time-consuming (2–6 days); lower sensitivity compared to RT-PCR.

**Serological Testing**

- **Target**: IgM/IgG antibodies
- **Advantages**: Useful for retrospective diagnosis and epidemiological studies.
- **Limitations**: Cross-reactivity with other enteroviruses; may not detect early infections.

**Enzyme-Linked Immunosorbent Assay (ELISA)**

- **Target**: viral antigens or antibodies
- **Advantages**: Can process large numbers of samples; relatively quick.
- **Limitations**: Potential for cross-reactivity; may require confirmation with other methods.

Netherlands
The Journal of Medicine



CASE REPORT

# Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection

**F. Fodili, E.F.H. van Bommel***

Department of Internal Medicine, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands, e-mail: e.f.h.vanbommel@asz.nl, * corresponding author

ABSTRACT

**Viral infections have been associated with a wide spectrum of muscle disorders, ranging from acute nonspecific myalgia to myositis. However, severe rhabdomyolysis, with or without accompanying acute renal failure (ARF), has been described only rarely. We report the fourth case in the literature of recent Coxsackie B virus infection complicated by severe rhabdomyolysis and ARF, necessitating temporary haemodialysis in a previously healthy young man. Although most Coxsackie B virus infections are asymptomatic, one should be aware of this potentially life-threatening complication of this virus. As illustrated with the present case, serological testing may reveal the diagnosis in a case of rhabdomyolysis after a viral illness.**

Despite immediate and vigorous hydration with normal saline and urine alkalisation with sodium bicarbonate to maintain a urine pH >7, the patient developed nonoliguric acute renal failure requiring temporary alternate-day haemodialysis three days after admission, which continued for two weeks (*figure 1*). Recovery was otherwise uneventful with a rapid decline in the serum creatine kinase (CK) level (*figure 1*), gradual disappearance of calf swelling and muscle pain, and almost complete recovery of renal function (creatinine on discharge from the hospital 150 µmol/l). At the time of his latest follow-up 18 months later, he had no further symptoms and the creatinine (108 µmol/l) remained stable.

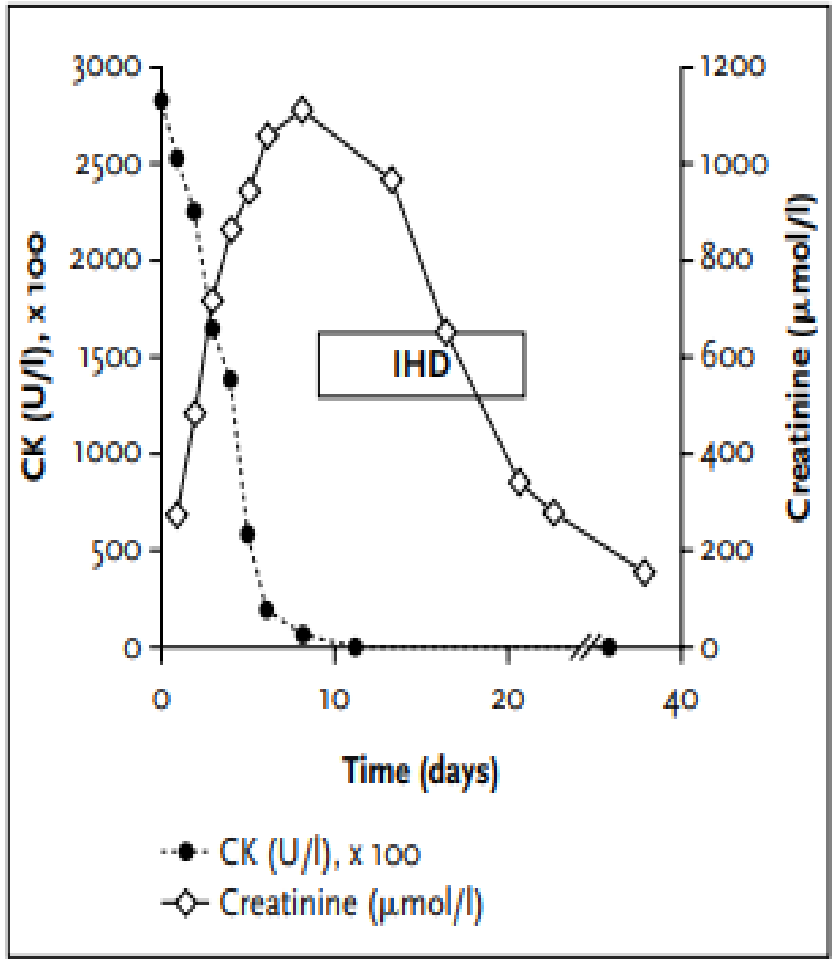
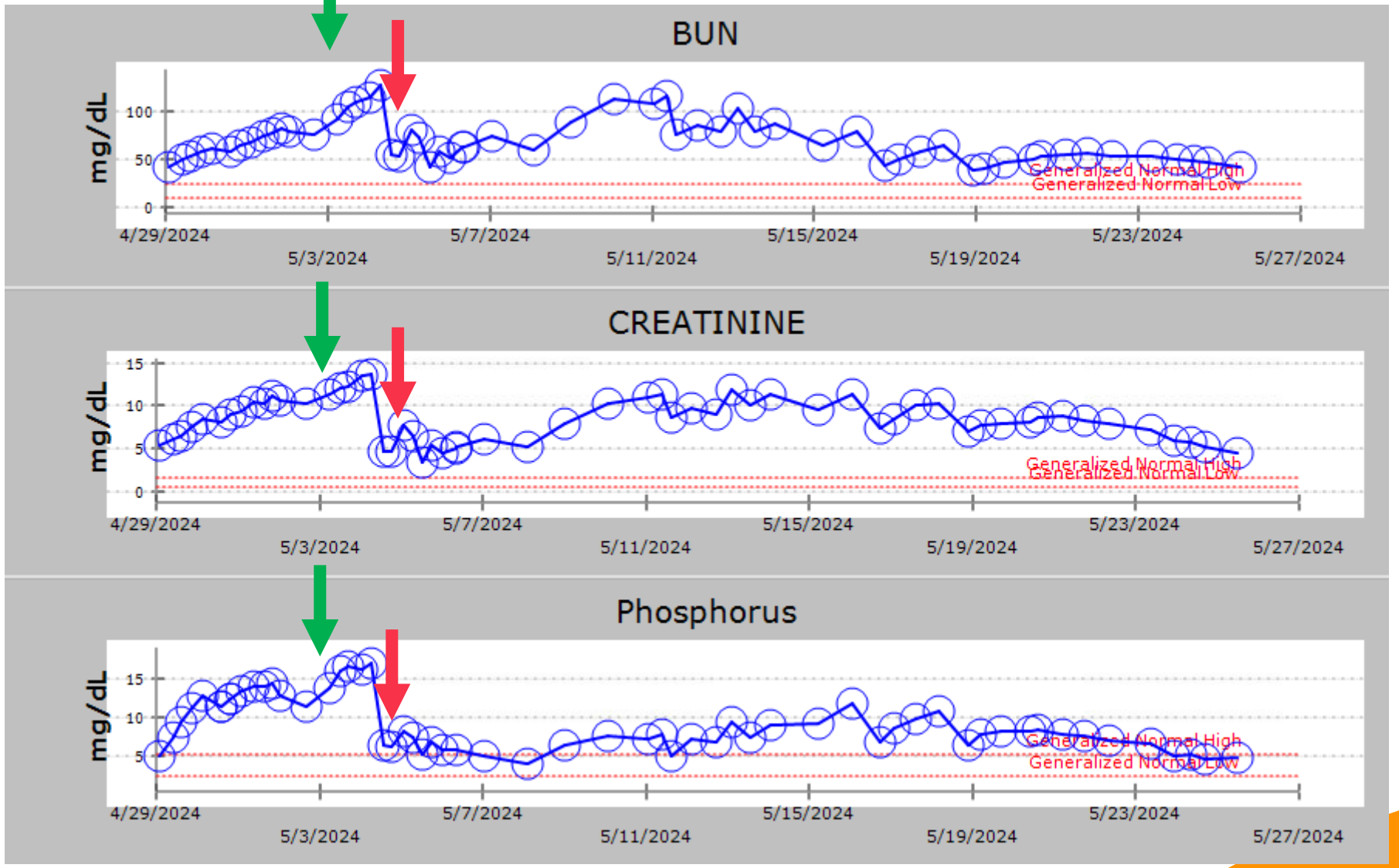



Figure 1

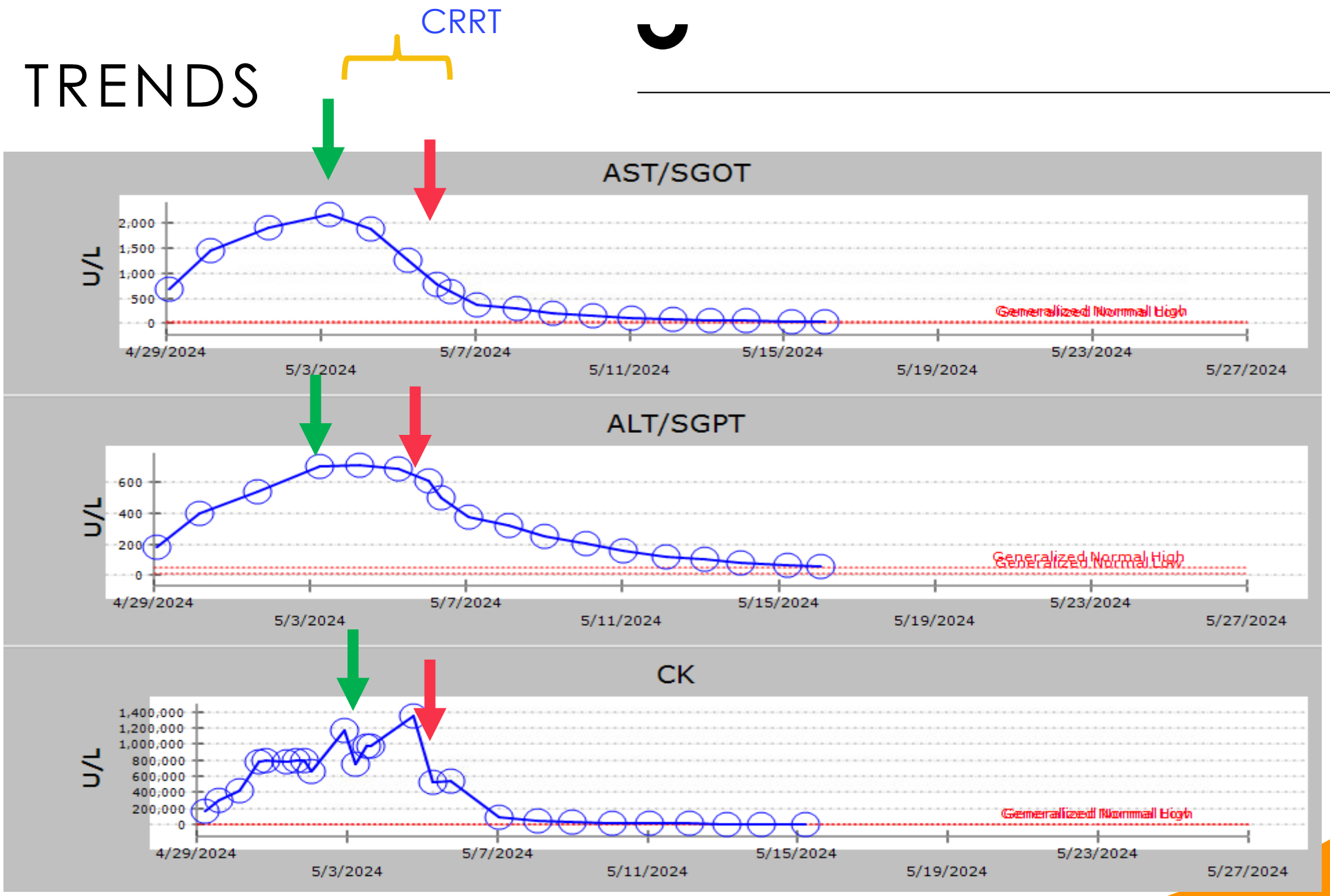
*Time course of serum creatine phosphokinase (CK) and creatinine levels*

# LAB TRENDS

CRRT



# LAB TRENDS


CRRT
AST/SGOT
U/L
2,000
1,500
1,000
500
0
Generalized Normal High
4/29/2024
5/3/2024
5/7/2024
5/11/2024
5/15/2024
5/19/2024
5/23/2024
5/27/2024
ALT/SGPT
U/L
600
400
200
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Generalized Normal High
Generalized Normal Low
4/29/2024
5/3/2024
5/7/2024
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CK
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1,400,000
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600,000
400,000
200,000
0
Generalized Normal High
4/29/2024
5/3/2024
5/7/2024
5/11/2024
5/15/2024
5/19/2024
5/23/2024
5/27/2024

# OUTCOMES

- Patient discharged 5/26
- Follow up with Nephrology
  - Kidney function returned to normal

# QUESTIONS ON THIS CASE?

# CASE 3

Biologist Blues

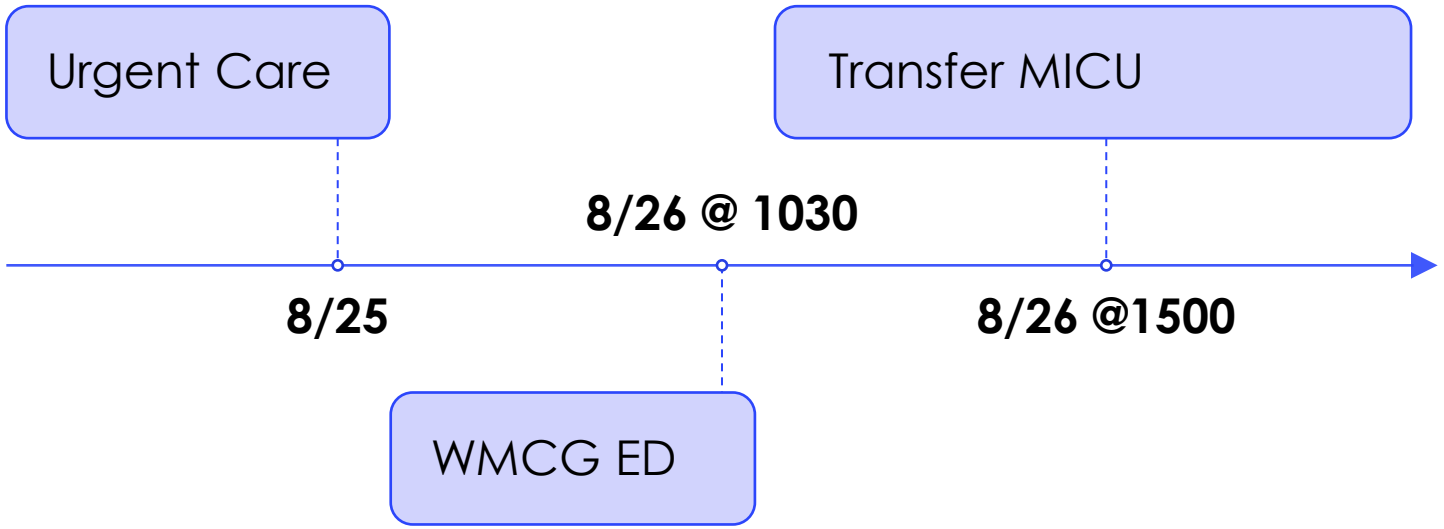
# CASE #3

- 73 yoM
- CC: SOB/Congestion. Recent travel from Netherlands. woke up this morning with mottling to nose and forehead.
- MedNow: COVID test = inconclusive
- Wife is asymptomatic.

# PROGRESSION

- AHRF
- Purpuric rash
- Pulmonary edema
- RLL PNA
- Ddx – shock with infectious etiology
- Admitted to MICU

**Clinical Timeline**



# MICU ADMISSION

H&P

- WBC = 4k, Segs = **%, Bands 44%, Plt = 16k
- D-dimer = 52,000, PT 30.2, INR 2.6, APTT 85
- NA 130, CO2 10, Mg 1.5
- BUN 50, CREA 3.45, Phos 7.9
- AST 2 400, ALT 1200
- LA 10.3
- Intubated

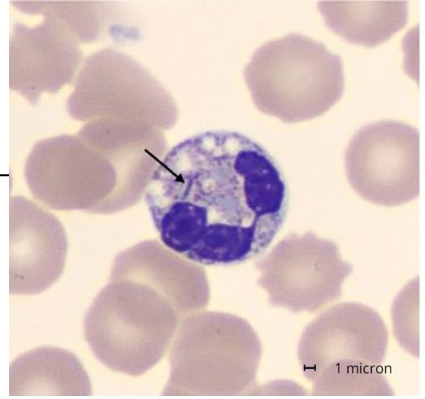
Exposure

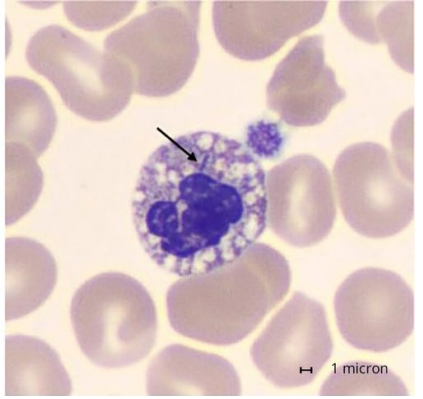
- International travel Netherland/Scotland
- Wildlife Biologist
- Known tick bites
- 3 dogs

#Concern for Ehrlichiosis

#Concern for Rocky Mountain Spotted Fever

# PATH//ID CONSULT




**ID Team A Pending Consult Note:**

Called and notified of peripheral smear concerning for maltese cross, raising concern for Babesiosis.

In brief, Mr. Vansant is a 73 year old male with no significant PMH who presented to WMCG with complaint of fevers, purpuric rash, chills, myalgias, diarrhea that started Saturday, originally believed to be secondary to COVID.

Based on history from obtained by primary team, the patient is a wildlife biologist with reported recent tick bite in GA while walking his dogs in the woods on his property. As an aside, he recently travelled to Scotland ~1 month ago.

**Recommendations**:
- Peripheral smear reviewed, with collections within the viewable neutrophil (not the RBC) that raised initially concern for Babesiosis and previously discussed with the team about potential coverage. After further discussion, infiltration of the neurophil would be more commonly seen in Anaplasmosis or Erlichosis and as a result, recommend continue Doxycycline 100mg IV twice daily pending serum studies and final pathologic report. No need for Atovaquone or Azithromycin at this time.
- Recommend sending a Tick Panel PCR (Ref Misc Lab TICKLB) from peripheral blood in a Lavender Top EDTA.

*** Final Report ***

Review of the peripheral blood smear reveals findings in accordance with the CBC data. Platelets are significantly suppressed in number. The ones noted, however, are morphologically unremarkable though some enlarged appropriately granulated forms are seen. The red blood cells are reduced in number (minimally), normochromic, and normocytic without pronounced anisopoikilocytosis, polychromasia, or rouleaux formation. However, occasional echinocytes are seen, which are typically artifactual in nature, and rare schistocytes are seen. The morphologic features are not typical for TTP. However, schistocytes are sometimes rare in DIC; therefore, given overall laboratory findings (i.e., elevated PT/PTT, suppressed fibrinogen, elevated D-dimer, undetectable haptoglobin), DIC is favored. Leukocytes are suppressed in number with a relative neutrophilia. An overt granulocyte left shift is seen with prominent toxic changes. In numerous neutrophils, rod shaped cytoplasmic inclusions are seen. These have the morphologic appearance of bacteria. The patient's chart is reviewed and ID consult is noted. Correlation with microbiology studies including cultures is suggested for further evaluation in this critically ill patient.

# WORK-UP

- 8/26 Blood Cx: no growth to date
- 8/26 BAL gram stain: Few neutrophils, Many yeast with pseudomycelia, Rare gram negative bacilli, Rare gram positive cocci, and Few squamous epithelial cells; culture no growth to date
- 8/26 Urine Cx: No growth to date
- 8/27 HIV: Negative
- 8/27 HCV Ab: Negative
- 8/27 strep pneumonia antigen: negative
- 8/29 RMSF IgG and IgM Negative and Positive Fungitell*

#Concern for Rickettsial Illness/Tick borne illness

#Concern for Capnocytophaga

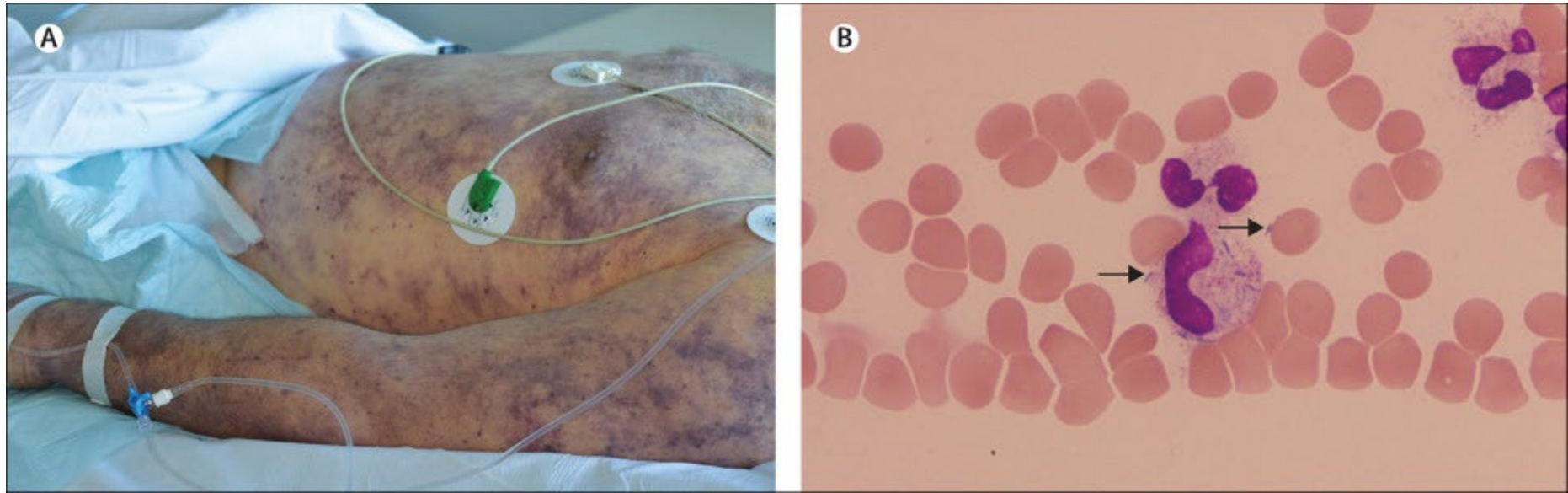
# TESTING FOR CAPNOCYTOPHAGA

**Traditional Cultures**

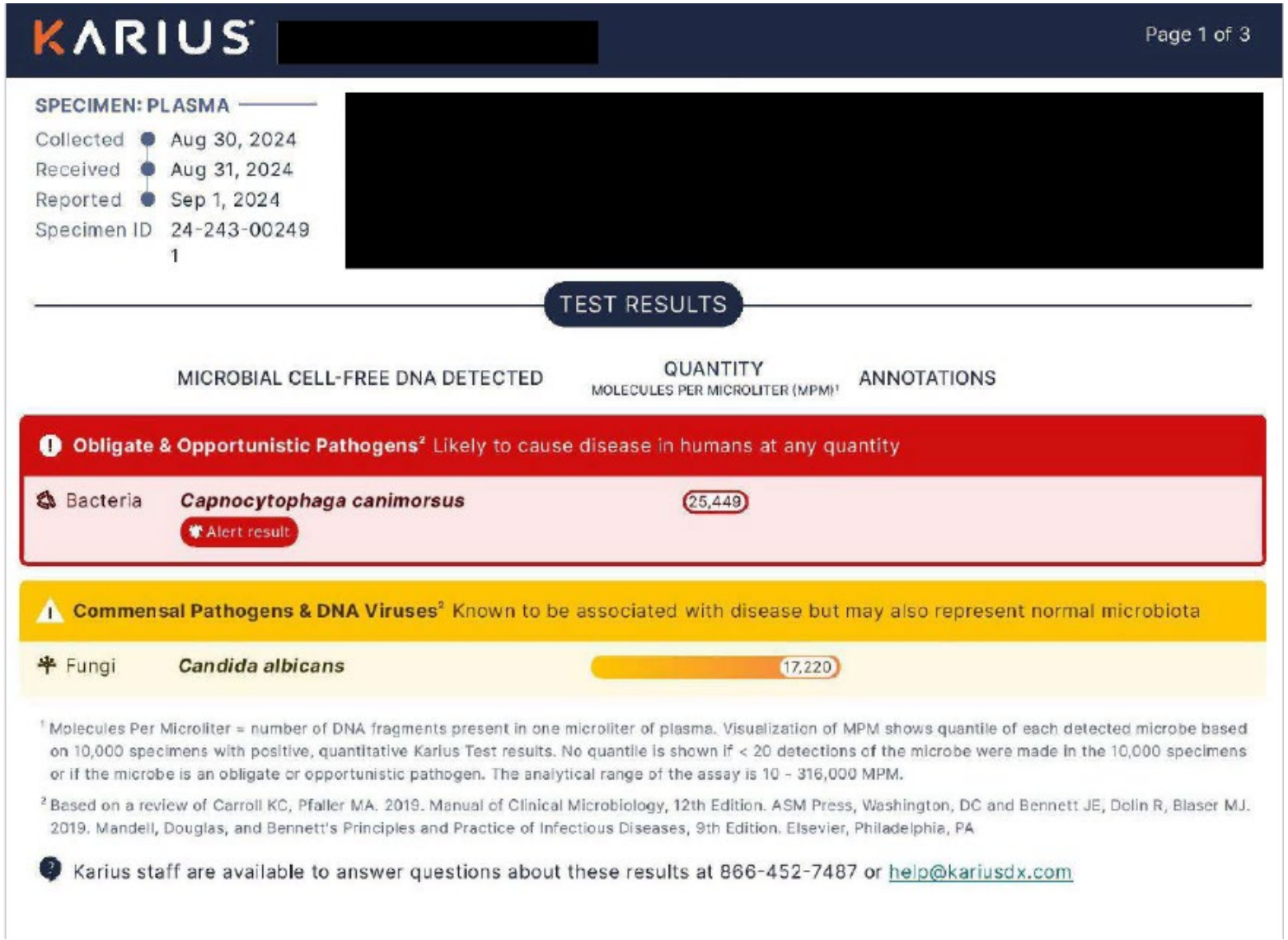
- Difficult to culture and identify in the lab
- Blood cultures accuracy is low

**Reliable Identification Methods**

- PCR (Polymerase Chain Reaction)
- 16S rRNA gene amplification
- MALDI-TOF mass spectrometry



# CONFIRMATION



KARIUS [redacted] Page 1 of 3

SPECIMEN: PLASMA

Collected Aug 30, 2024
Received Aug 31, 2024
Reported Sep 1, 2024
Specimen ID 24-243-00249 1

[redacted]

TEST RESULTS

| MICROBIAL CELL-FREE DNA DETECTED | QUANTITY MOLECULES PER MICROLITER (MPM)[1] | ANNOTATIONS |
|---|---|---|
| **Obligate & Opportunistic Pathogens**[2] Likely to cause disease in humans at any quantity | | |
| Bacteria *Capnocytophaga canimorsus* Alert result | 25,449 | |
| **Commensal Pathogens & DNA Viruses**[2] Known to be associated with disease but may also represent normal microbiota | | |
| Fungi *Candida albicans* | 17,220 | |

[1] Molecules Per Microliter = number of DNA fragments present in one microliter of plasma. Visualization of MPM shows quantile of each detected microbe based on 10,000 specimens with positive, quantitative Karius Test results. No quantile is shown if < 20 detections of the microbe were made in the 10,000 specimens or if the microbe is an obligate or opportunistic pathogen. The analytical range of the assay is 10 - 316,000 MPM.

[2] Based on a review of Carroll KC, Pfaller MA. 2019. Manual of Clinical Microbiology, 12th Edition. ASM Press, Washington, DC and Bennett JE, Dolin R, Blaser MJ. 2019. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th Edition. Elsevier, Philadelphia, PA

Karius staff are available to answer questions about these results at 866-452-7487 or help@kariusdx.com

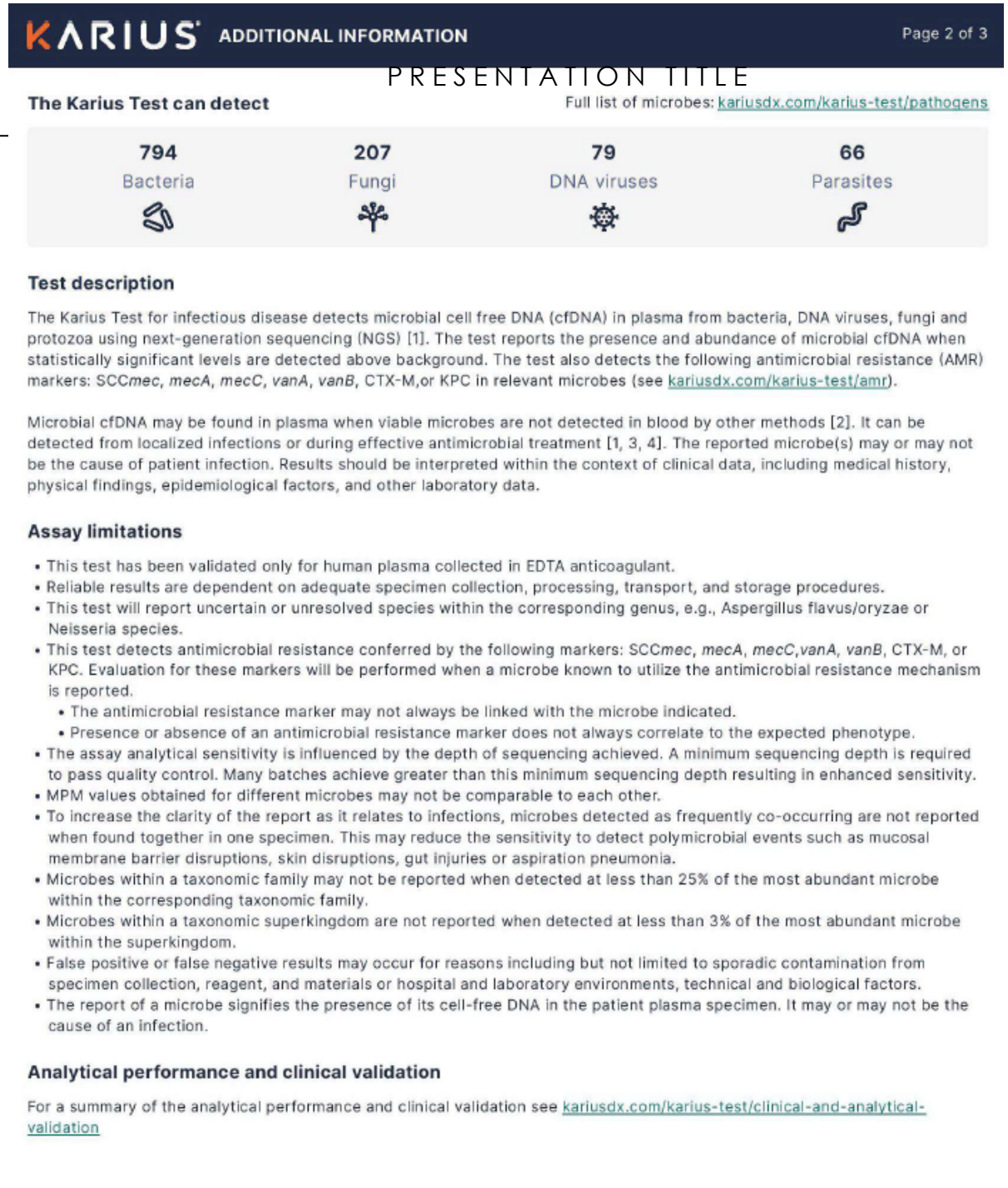
# OUTCOMES

- Multi-organ failure due to septic shock
  - DIC – requiring FFP, cryo, plt transfusions
- Meropenem to treat Capnocytophaga
  - Allergic reaction: hypotensive, sloughing rash
  - Switch to Ciprofloxazin 400 Q12, Metronidazole 500 Q8, and Doxycycline 100 mg Q12.
- Candida Albicans Fungemia
  - IV micafugin 100 mg
- large MCA infarct with midline shift
  - Expired 9/9

# ABOUT THE KARIUS TEST

- **Comprehensive Detection**: 1000+ pathogens
- **Rapid Results**: 24 to 36 hours
- **Non-Invasive**: blood draw
- **Cost:** ~$2,000
- **Impact**: more accurate diagnoses & timely treatments.





KARIUS ADDITIONAL INFORMATION Page 2 of 3

**The Karius Test can detect**

Full list of microbes: kariusdx.com/karius-test/pathogens

| 794 | 207 | 79 | 66 |
|---|---|---|---|
| Bacteria | Fungi | DNA viruses | Parasites |

**Test description**

The Karius Test for infectious disease detects microbial cell free DNA (cfDNA) in plasma from bacteria, DNA viruses, fungi and protozoa using next-generation sequencing (NGS) [1]. The test reports the presence and abundance of microbial cfDNA when statistically significant levels are detected above background. The test also detects the following antimicrobial resistance (AMR) markers: SCC*mec*, *mecA*, *mecC*, *vanA*, *vanB*, CTX-M,or KPC in relevant microbes (see kariusdx.com/karius-test/amr).

Microbial cfDNA may be found in plasma when viable microbes are not detected in blood by other methods [2]. It can be detected from localized infections or during effective antimicrobial treatment [1, 3, 4]. The reported microbe(s) may or may not be the cause of patient infection. Results should be interpreted within the context of clinical data, including medical history, physical findings, epidemiological factors, and other laboratory data.

**Assay limitations**

- This test has been validated only for human plasma collected in EDTA anticoagulant.
- Reliable results are dependent on adequate specimen collection, processing, transport, and storage procedures.
- This test will report uncertain or unresolved species within the corresponding genus, e.g., Aspergillus flavus/oryzae or Neisseria species.
- This test detects antimicrobial resistance conferred by the following markers: SCC*mec*, *mecA*, *mecC*,*vanA*, *vanB*, CTX-M, or KPC. Evaluation for these markers will be performed when a microbe known to utilize the antimicrobial resistance mechanism is reported.
  - The antimicrobial resistance marker may not always be linked with the microbe indicated.
  - Presence or absence of an antimicrobial resistance marker does not always correlate to the expected phenotype.
- The assay analytical sensitivity is influenced by the depth of sequencing achieved. A minimum sequencing depth is required to pass quality control. Many batches achieve greater than this minimum sequencing depth resulting in enhanced sensitivity.
- MPM values obtained for different microbes may not be comparable to each other.
- To increase the clarity of the report as it relates to infections, microbes detected as frequently co-occurring are not reported when found together in one specimen. This may reduce the sensitivity to detect polymicrobial events such as mucosal membrane barrier disruptions, skin disruptions, gut injuries or aspiration pneumonia.
- Microbes within a taxonomic family may not be reported when detected at less than 25% of the most abundant microbe within the corresponding taxonomic family.
- Microbes within a taxonomic superkingdom are not reported when detected at less than 3% of the most abundant microbe within the superkingdom.
- False positive or false negative results may occur for reasons including but not limited to sporadic contamination from specimen collection, reagent, and materials or hospital and laboratory environments, technical and biological factors.
- The report of a microbe signifies the presence of its cell-free DNA in the patient plasma specimen. It may or may not be the cause of an infection.

**Analytical performance and clinical validation**

For a summary of the analytical performance and clinical validation see kariusdx.com/karius-test/clinical-and-analytical-validation

# QUESTIONS ON THIS CASE?

# REFERENCES

1. https://www.cdc.gov/dpdx/freelivingamebic/index.html
2. https://www.njmonline.nl/getpdf.php?id=51
3. https://www.cdc.gov/capnocytophaga/hcp/clinical-overview/index.html

# THANK YOU

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