ONCE BITTEN, TWICE SICK

MATTHEW PULLEN MD

OUR PATIENT:

- 83-year old white male
- Brought to ER by his wife for fever and recurrent altered mental status
- Had two recent admission for similar symptoms wthin the Fairview system (more on those later)
- On presentation, his temperature was recorded as high as 104.4 F. He was fairly confused, responding to most questions with rambling nonsensical answers and trying to get out of bed without any real direction or motive. Could not name date, place, or reason for being admitted.

BACKGROUND INFORMATION

- PMHx: HTN, CAD (with PCI of LCx and RCA), DM2, RA, BPH, HLD,
- PSHx: C6-C7 fusion, right wrist carpal tunnel surgery
- SHx: Married and lives with his wife in Zimmerman, MN. No history of tobacco, alcohol, or illicit drug use.

ADMISSION # 1

- His first admission occurred after a fall resulting in minor facial trauma. He was admitted for overnight observation, then developed fever and confusion concerning for sepsis of unknown origin.
- Cultures of blood and urine were unrevealing
- CT chest was clear. Only finding on CT abdomen was gallstones without signs of cholecystitis.
- Over the first few days, he developed leukopenia, thrombocytopenia, and a mild AST elevation as his confusion and fever worsened.
- After developing mild RUQ pain, repeat abdominal imaging (U/S this time) showed possible gallbladder wall thickening and previously seen gallstones.
- Patient was treated for sepsis thought to be due to cholecystitis: vancomycin and zosyn, with transition to Augmentin x 7 days at discharge to TCU.

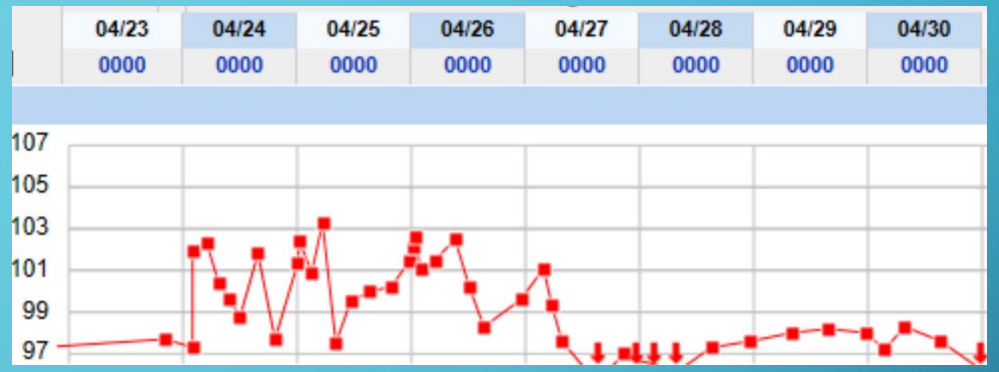
ADMISSION # 2

- 6 days after discharge to TCU, the patient returned to the ER from TCU with worsening fever (up to 104) and waxing/waning confusion (never fully resolved). Denied abdominal pain.
- LP performed demonstrating: 0 WBC (58% Monos, 40% Lymphos), glucose 82 mg/dL, protein 89 mg/dL, 25 RBC
- WBC had dropped to 1.6 from 3.5 the day prior at the TCU and Plt dropped to 70k from 127k in prior admission. AST remained elevated (no other LFT elevations).
- Started on vancomycin and zosyn again based on previous marginal improvement last admission.
- HIDA scan showed GB EF of 5%. Surgeons did not feel comfortable taking him to the ER or putting in a percutaneous tube given fevers.
- As in previous admission, blood and urine cultures were negative, imaging was unrevealing. Lyme Ab tested and negative, no other rickettsial work-up performed.
- Given lack of improvement and unclear etiology, patient was transferred to University

DOWN THE ROAD TO THE UNIVERSITY…

- On arrival, new labs are collected:
  - CRP 173 (previous was <2.9 on 4/20)
  - Procalcitonin 5.7 (no previous level)
- Patient is started on meropenem (was on vancomycin/zosyn on transfer) due to concern that zosyn could be contributing to leukopenia
- In addition to new blood cultures, a malignancy work-up is started given cytopenias: SPEP/UPEP, peripheral blood smear
- ID is consulted to explore other possible etiologies of fever, confusion, and leukopenia

LEUKOPENIA, THROMBOCYTOPENIA, FEVER



	WBC
Ref. Range	Latest Ref Range: 4.0 - 11.0 10e9/L
4/20/2017 1700	6.5
4/23/2017 2025	4.4
4/24/2017 0258	4.8
4/25/2017 0536	3.3 ▼
4/26/2017 0555	2.5 ▼
4/27/2017 0528	2.5 ▼
4/28/2017 0510	3.8 ▼
4/29/2017 0535	5.1
4/30/2017 0600	6.9
5/7/2017 2010	5.8
5/8/2017 0540	5.4
5/9/2017 0550	3.5 ▼
5/10/2017 0610	1.6 ▼

	Platelet Count
Ref. Range	Latest Ref Range: 150 - 450 10e9/L
4/20/2017 1700	203
4/23/2017 2025	174
4/25/2017 0536	113 ▼
4/26/2017 0555	77 ▼
4/27/2017 0528	59 ▼
4/28/2017 0510	70 ▼
4/29/2017 0535	106 ▼
4/30/2017 0600	158
5/7/2017 2010	262
5/8/2017 0540	208
5/9/2017 0550	127 ▼
5/10/2017 0610	78 ▼

PHYSICAL EXAMINATION

- No rashes or lesions visible anywhere. No abdominal pain, no localizing symptoms at all apart from CNS. Lungs were clear, heart sounds intact and normal, bowel sounds present with no organomegaly, no cervical, axillary, or inguinal lymphadenopathy.
- Temperature was 102.7F the morning of the consultation.
- Mental status was still very altered. He was pleasant, but could not provide coherent answers, constantly picked at devices and skin, tried to get out of bed.

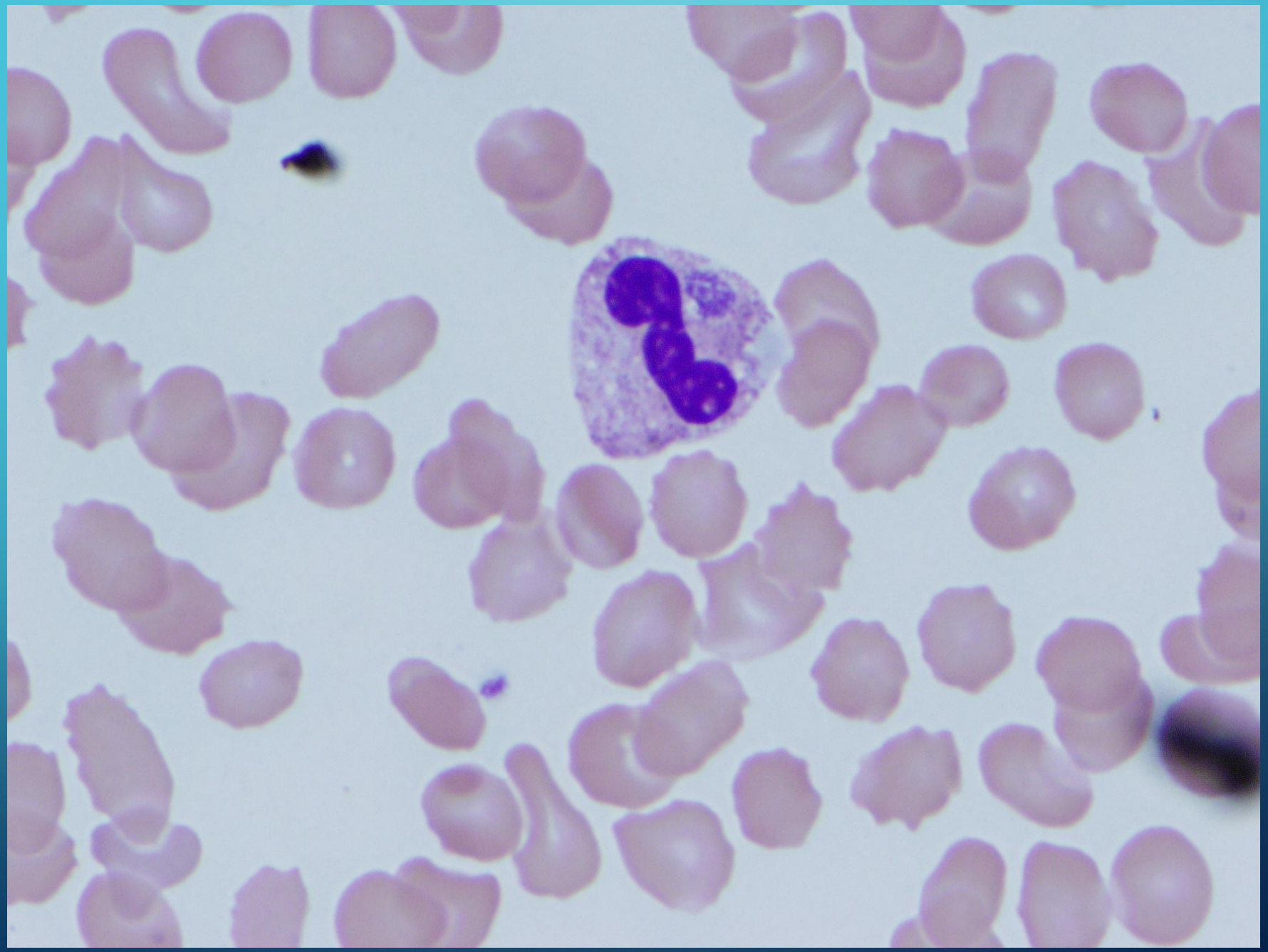
DIFFERENTIALS?

- Occult abscess?
- Hematologic malignancy?
- Cholecystitis?
- Aseptic meningitis?
- Rickettsial disease?
- Rheumatologic disorder?
- Before any of our work-up was even collected, the hematopatholgist called with a fairly conclusive finding…

EXPOSURE HISTORY

- Wife states the patient isn't "an outdoorsman", but they do occasionally go for walks
- Unsure if he has had tick or mosquito bites
- No pets or wild animal contacts
- No sick contacts
- No foreign travel

Location of patient's home near Sherburn National Wildlife Refuge



RECOMMENDATIONS

- After discussion with primary team, doxycycline was added to the patient's regimen
- Recommended expanded rickettsial testing
  - Lyme IgG/IgM/PCR
  - Babesia IgG/IgM/PCR
  - Anaplasma IgG/IgM/PCR)

ANAPLASMA PHAGOCYTOPHAILUM

- Obligate intracellular gram-negative bacterium that makes up part of the 7 known agents of Ehrliciosis in North America and Europe
  - Anaplama phagocytophilum = Human granulocytis anaplasmosis (HGA)
  - Ehrlichia chaffeensis = Human monocytic Ehrlichiosis (HME)
  - Ehrlichia ewingii = Human ewingii Ehrlichosis (HEE)
  - Ehrlichia muris-like agent (EMLA)
  - Panola Mountain Ehrlichia (similar to the non-human Ehrlichia ruminates)
  - Ehrlichia canis (thought to be limited to dogs, but implicated in some human cases)
  - Neoehrlichia mikurensis
- Focus of this talk will be differentiating between Ehrlichia chaffeensis/ewingii and Anasplama, given geographic overlap here.

HUMAN MONOCYTIC EHRLICHIOSIS

- Discovered in 1986
- Main reservoir is the white-tailed deer. The transmitting organisms is the Amblyomma americanum tick (Lone Star tick).
  - This tick also transmits Ehrlichia ewingii, Southeri Tick-Associated Rash Illness (STARI), Francisella tularensis, and to a very limited extent, Borrellia Burgdorferi. Also associated with development of galactose-alpha-1,3-galactose non-primate meat allergy.
- Once in the human body, resides within monocytes (hence the name). The form vacuoles and remain within these (unlike Rickettsia species which live freely in the cell cytoplasm).
  - Within the vacuole, clusters of bacteria form called “morula”, which contain replicating forms and infective forms of Ehrlichia.

HUMAN GRANULOCYTIC ANAPLASMOSIS

- Discovered in 1994, previously known as Human Granulocutic Ehrlichosis until it was recognized as being caused by a different organisms
- Main reservoirs are small mammals (white-footed mice), with main tick transmitter being the Ixodes scapularis and Ixodes pacificus ticks in North America.
- Unlike Ehrlichis, this organisms resides in neutrophils within the human body. However, like Ehrlichia, Anaplasma forms vacuoles inside the neutrophils and has a similar life cycle.

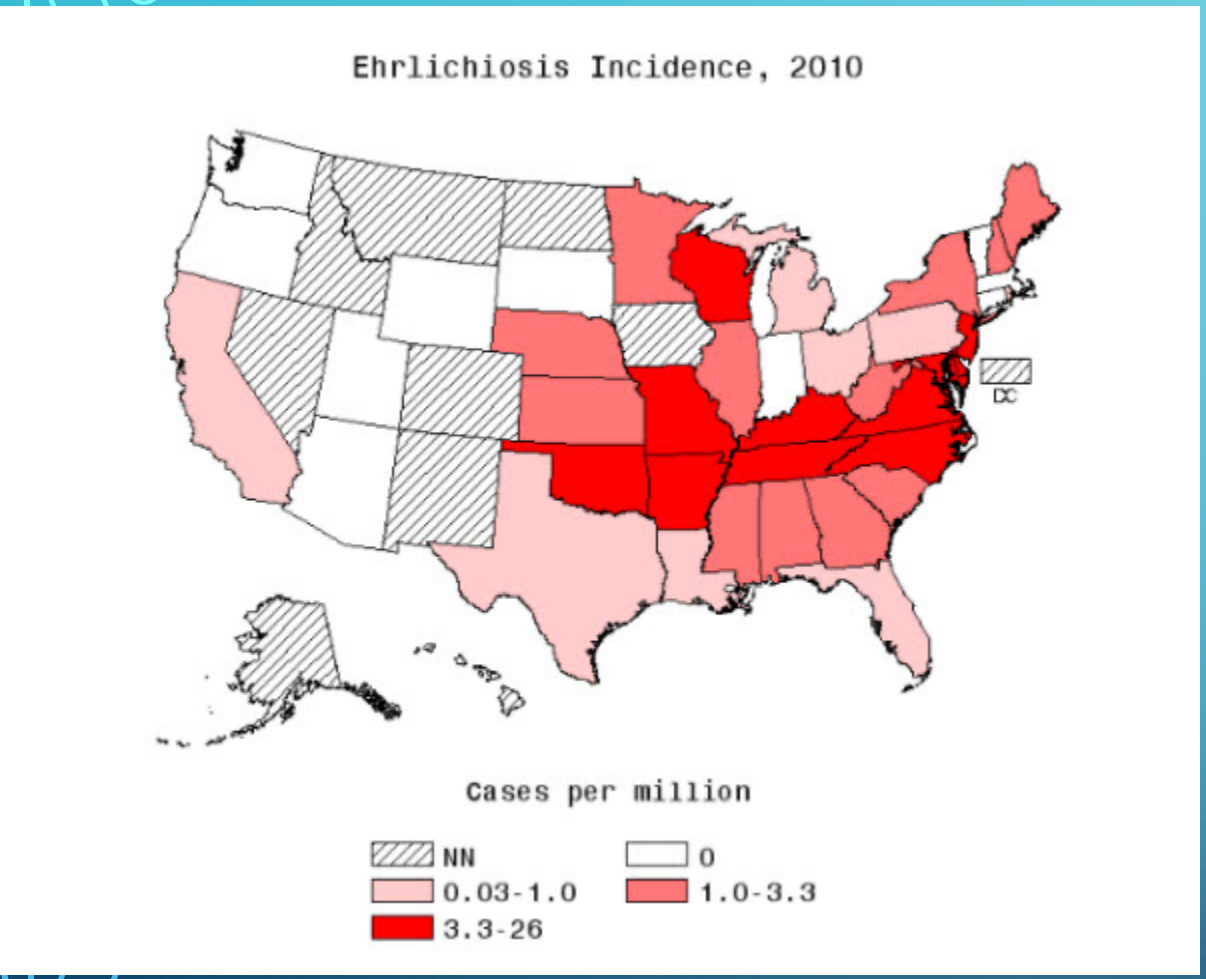
MECHANISMS OF INFECTION

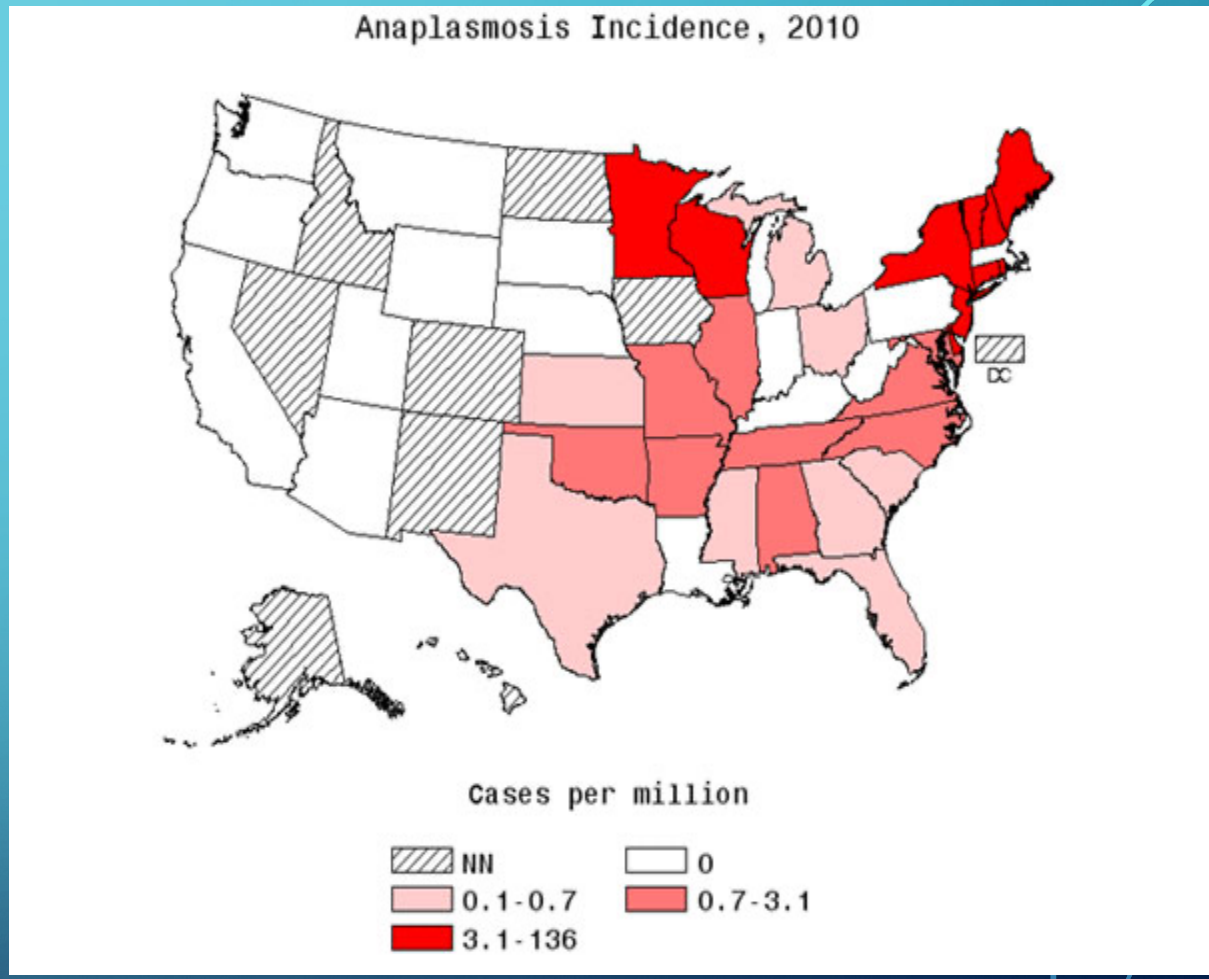
HME

- Once tick bite occurs, spreads by lymphatic and circulatory system to nodes, marrow, and any other tissue with high levels of mononuclear cells
- Can cause thrombocytopenia, leukopenia, and anemia, as well as focal hepatocellular injury, nodal injury, splenic injury (all areas high in mononuclear cells).
- Low burden of bacteria can cause significant disease which, in mouse models, seems to be due to proinflammatory state and cytokine release triggered by the bacteria, rather than a direct effect of the organism itself.
- Fatal disease often the result of multi-ordan involvement and injury (spleen, liver, marrow), though most effect is from the host immune/inflammatory response.

HGA

- Tick bite and resulting inflammatory response brings neutrophils to the site, which are then infected by Anasplama
- Infected neutrophils have an impaired ability to travel and kill internally and phagocytise, though they can still degranulate.
- Also causes leukopenia, thrombocytopenia, and anemia.
- However, unlike HME, is often associated with erythrophagocytosis on histopathology, and in more extreme cases can present with a pneumonitis and/or pulmonary hemorrhage.
- Like HME, can cause focal hepatocellular injury and splenic injury.


Ehrlichiosis Incidence, 2010
DC
Cases per million
NN
0
0.03-1.0
1.0-3.3
3.3-26


Anaplasmosis Incidence, 2010
DC
Cases per million
NN
0
0.1-0.7
0.7-3.1
3.1-136

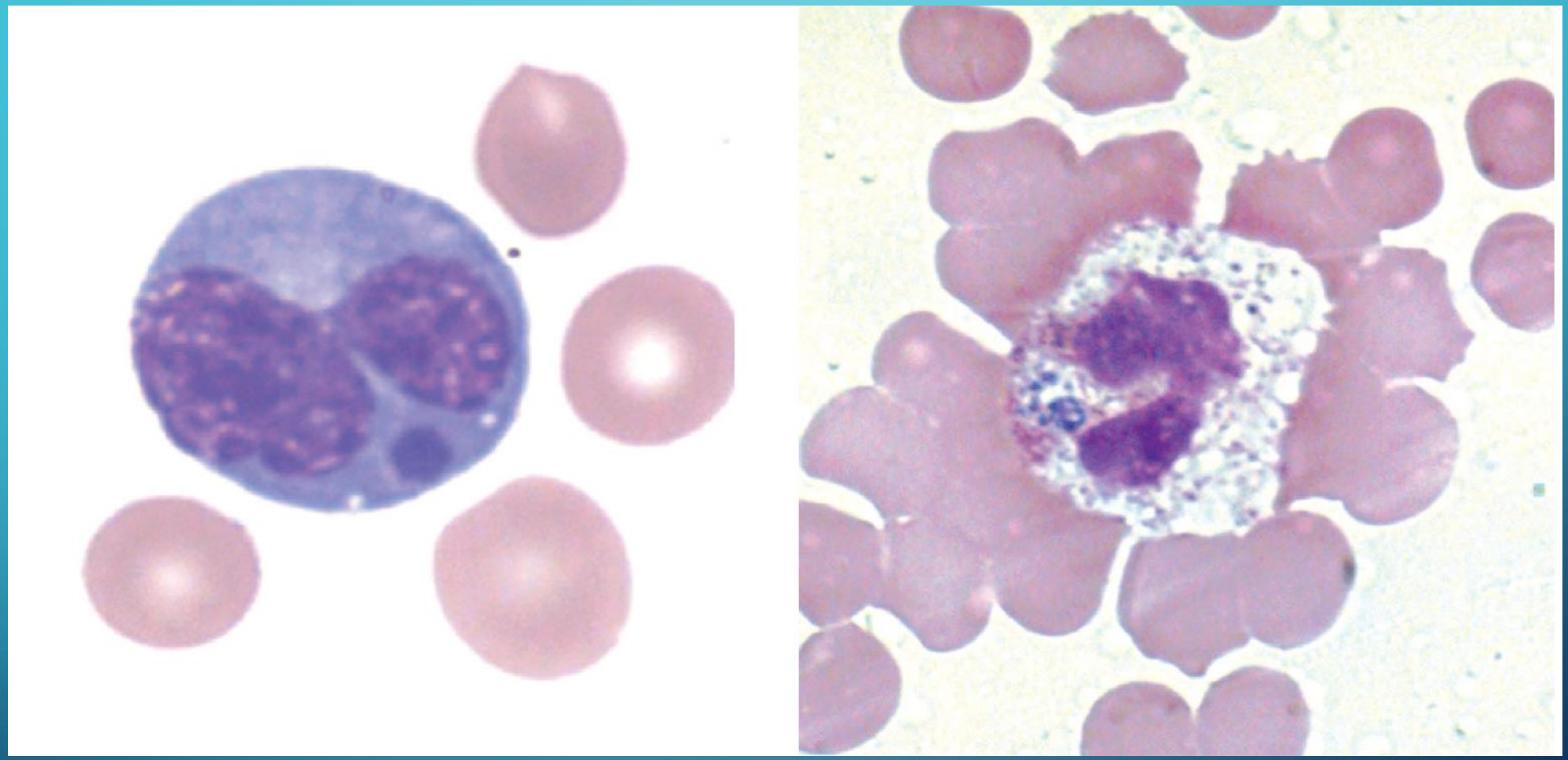
PRESENTATION AND DIAGNOSIS

HME

- Most often presents with headache, fevers/chills, myalgias, malaise, and GI complaints
- Only about 1/3 of patients (mostly children) develop a rash, with a wide variation in type and distribution.
- Cytopenias, increased serum transaminases
  - WBC nadir usually 1.3-4, Plt nadir around 50k-140k.
- Diagnosed most often by antibody ond/or PCR assays. Rarely seen on peripheral smear early in disease, easier to spot in severe or late disease smears of highly infected tissue
- Can result in severe illness or death due to multiorgan dysfunction.
  - ~3-5% will seek medical attention. Severity increases with age and comorbidities (HIV, transplant, immunosuppression, splenectomy)

HGA

- Like HME, associated with headache, fevers/chills, myalgias, malaise.
- Less likely to present with GI symptoms, and only about 10% present with any rash symptoms.
- Like HME, usually diagnosed with antibody and PCR assays. Harder to spot on HME because it produces lower blood and tissue burden.
- More often than not, it is a self-limited disease. Severe or fatal disease is rare, typically associated with DIC-like syndromes, renal failure, or pulmonary hemorrhage.



LEFT: HME

RIGHTL HGA

TREATMENT

- Vitamin D!
  - Doxycycline 100mg BID
  - IV therapy indicated if patient is critically ill, or unable to take PO. Otherwise, PO is appropriate.
- Both diseases should show improvement in fever and symptoms within 24-48 hours of doxycycline intiation if the disease is in an early stage (can take several days if late stage), but duration of therapy is differnt.:
  - HME – treat for length of fever + about 3 days after fever subsides and symptoms begin improving
  - HGA – should be treated for a total of 10 days due to risk of co-infection with B. burdorferi (same tick, about 25-30% co-carriage rate in some studies)
- Very few alternatives to doxycycline.
  - Chloramphenicol works for RMSF but no Ehrlichosis/Anaplasmosis, and is associated with higher risk of death
  - Rifampin/Rifamycins show in vitro efficacy against Ehrlichia and Anasplama, a a few small trials in pregnant women and children show promise. Does not treat for co-infection with B. burgdorferi
  - Beta-lactams do not work.
  - E. chafeensis has resistance to FQ and Anasplama has high relapse rate with FQ)particularly levofloxacin).

PATIENT PROLOGUE

- Defervesced within 24 hours of starting doxycycline
- WBC rose from 1.6 to 5.1 within 72 hours
- Plt rose from 78k to 200k in one week
- Discharge 5 days after transfer with planned total course of 14 days of doxycycline.
- Still had some confusion at the time of discharge (knew he was in a hospital in Minneapolis, but time and situation were foggy)
  - Has had slow improvement, though at last note from a few days ago, still has periods of confusion which may be masked by multiple sedating drugs being given at nursing home.

REFERENCES

- “CDC – Anaplasma” and “CDC – Ehrlichia” https://www.cdc.gov
- Clinical Infectious Diseases
- Up-To-Date