Brigham and Women's Hospital
Founding Member, Mass General Brigham

# Hot Topics in Infectious Diseases

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CONTINUING MEDICAL EDUCATION
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HARVARD MEDICAL SCHOOL
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# Disclosures

- I have research funding from Cidara, Mundipharma, F2G, Scynexis and GSK
- I have been a consultant for Melinta, Pfizer, Roche, Seres therapeutics, Takeda and Treeline biosciences

# What's New in Infectious Diseases?

- Formidable New & Old Bugs
  - Measles
  - Avian influenza
  - Resistant dermatophyte infection with new mode of spread
  - Powassan and other vector-borne illnesses
- New Antimicrobials
  - Gepotidacin 2025
  - Sulopenem etzadroxil+probenecid 2024
  - Cefepime-enmetazobactam 2024
  - Ceftobiprole 2024
  - Rezafungin 2023
  - SER-109 2023
- New Problems
  - Impact of climate change on infection
- New Guidelines for Testing and Management
  - COVID-19 2025
  - Antimicrobial resistance 2024
  - New Fever in Critically Ill Patients 2023
  - Diabetic Foot Infection 2023
- New Approach to Old Problems
  - Oral antibiotics for serious invasive infection
  - Shorter antimicrobial courses for bloodstream infection

# Learning objectives

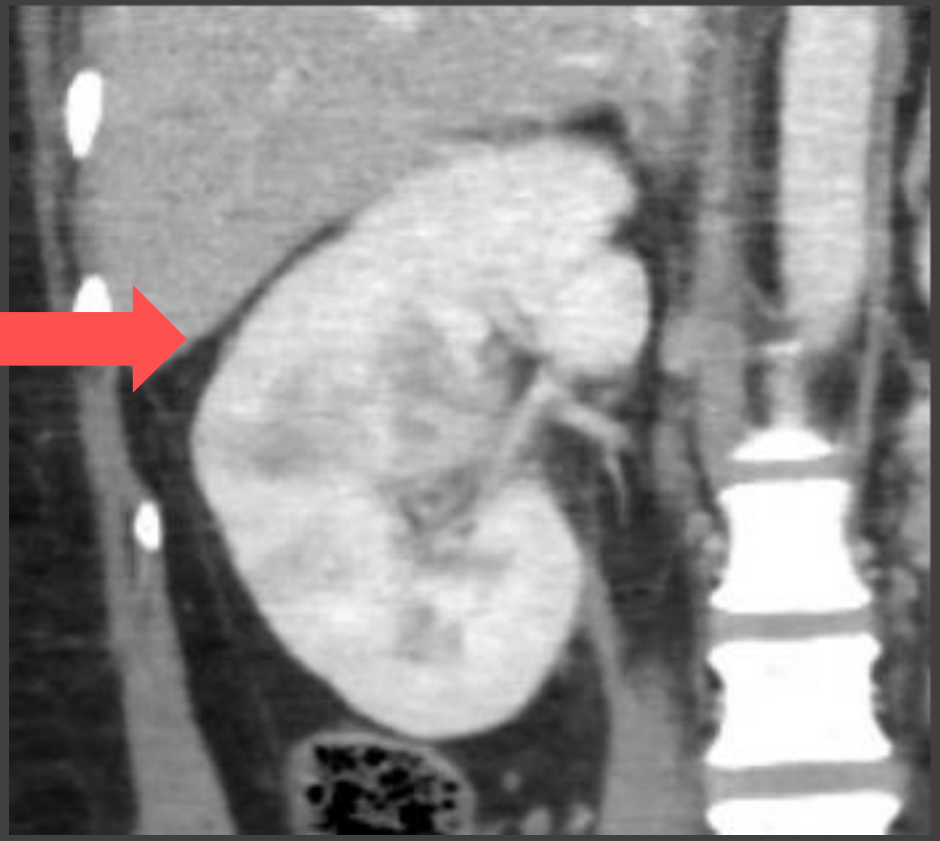
1. To learn when it is appropriate and safe to use oral antibiotics for gram negative bacteremia and that the best antibiotic choices are
2. To learn when it is apporpaite to treat bacteremia with a short (7 day) course of antibiotics
3. To develop an understanding of the current and potential impact of climate change on infection risk
4. To learn the basic epidemiology and presentation of Powassan infection

# New Approach to Old Problems:

Oral antibiotics for serious invasive infections

# Clinical Question

- A 35-year-old woman with obesity and recurrent UTI presents with fever to 103F, tachycardia, hypotension and right flank pain
  - CT imaging consistent with pyelonephritis
- She is admitted to the ICU where she requires pressors for <12 hours
- Improves on empiric cefepime
- 4 of 4 **Blood cultures** and **urine culture** from admission grow **E coli**
  - Subsequent blood cultures negative
- She is afebrile, normotensive and ready for discharge 3 days later



# What's the best antibiotic regimen for discharge home on hospital day 4?

- E coli urine susceptibilities
  - Ampicillin resistant
  - Cefazolin susceptible
  - Cefepime susceptible
  - Ceftriaxone susceptible
  - Ciprofloxacin resistant
  - Levofloxacin resistant
  - Nitrofurantoin susceptible
  - Trimethoprim-sulfamethoxazole susceptible

A. Oral nitrofurantoin x5 days
B. IV ceftriaxone x6 days
C. Oral trimethoprim-sulfa x6 days
D. Oral amoxicillin x10 days
E. Oral cephalexin x10 days

# A shift to oral antibiotics for serious infection?

- Historically serious invasive infections in adults have been treated with parenteral antibiotics
- However, benefits of avoiding long term IV therapy make oral therapy appealing
  - Oral therapy can reduce length of hospital stay, improve mobility, reduce cost
  - Complications of IV therapy include catheter-related infection, line-associated DVT, cost associated with line care
- Areas where there is increasing interest in using oral antibiotics as "step-down" therapy includes
  1. Gram-negative bacteremia (GNB)
  2. Endocarditis
  3. Bone and joint infection in adults

Iversen K, et al. N Engl J Med. 2019;380:415-24
Li H-K, et al. N Engl J Med. 2019;380:425-36.
Boucher HW. N Engl J Med. 2019;380:487-9.

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  3. Bone and joint infection in adults

Important studies have demonstrated the feasibility but oral step-down antibiotics for these infections is an area of emerging practice change and study!

Iversen K, et al. N Engl J Med. 2019;380:415-24
Li H-K, et al. N Engl J Med. 2019;380:425-36.
Boucher HW. N Engl J Med. 2019;380:487-9.

# Oral Antibiotics: Basic Principles

- Certain antibiotics have excellent oral bioavailability such that oral therapy achieves similar concentrations to IV (eg. levofloxacin)
  - In some cases where oral bioavailability is less, increased dose of oral agent can overcome lower bioavailability (eg. Ciprofloxacin→ 400 IV = 750mg po)
  - In some cases oral bioavailability is good, but oral dosing is limited by side effects (eg. Clindamycin IV is given at higher doses than can be given orally)
- Oral antibiotics at standard dose with similar concentrations to IV:
  - Levofloxacin, Ciprofloxacin, Moxifloxacin
  - Trimethoprim-Sulfamethoxazole (TMP-SMX)
  - Metronidazole
  - Linezolid
  - Clindamycin (but hard to tolerate at appropriate dose)

Beique L, Zvonar R. Can J Hosp Pharm. 2015;68:318-26.

# Oral Antibiotics: Gram-Negative Bloodstream Infection

- Tamma, et al. studied a propensity score-matched cohort of 1478 patients with **Enterobacteriaceae** and adequate source control at 3 hospitals
  - GNB sources: Urinary tract (40%), GI tract (20%) catheter-associated (18%), pulmonary (4%), SSTI (3%)
  - Microbiology: *E. coli* 44%, *Klebsiella spp.* 36%, *Enterobacter spp.* 12%
- No difference in 30-day mortality or recurrent bacteremia between those treated with oral 'step-down' therapy within 5 days vs. parenteral therapy
  - Recurrent bacteremia was rare in both groups (<1% in both groups)
- Median time from bacteremia to hospital discharge was significantly shorter in the oral therapy group (5 days vs. 7 days, HR 0.98)
- 84% in the oral step-down group were treated with antibiotics with high oral bioavailability→ the large majority of which were fluroquinolones
  - Low number of patients treated with low bioavailability oral antibiotics limited statistical power to address the importance of bioavailability
  - Minority of patients were immunocompromised

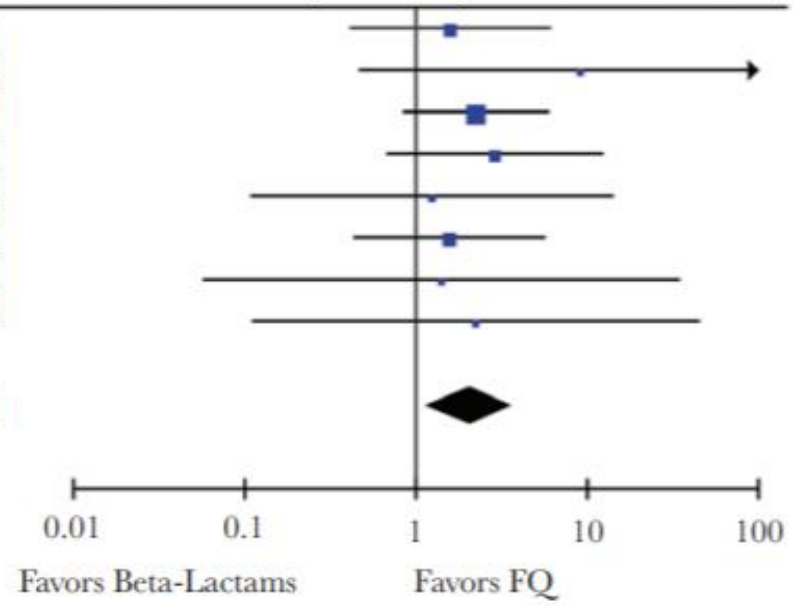
Tamma PD, et al. JAMA Intern Med 2019;179:316-23.

A

| Study or Subgroup | BL Events | BL Total | FQ Events | FQ Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Fong 2018 | 4 | 59 | 5 | 114 | 17.4% | 1.59 [0.41, 6.14] |
| Gumbleton 2018 | 3 | 86 | 0 | 108 | 3.6% | 9.10 [0.46, 178.52] |
| Kutob 2016 | 7 | 77 | 11 | 257 | 32.9% | 2.24 [0.84, 5.98] |
| Mercuro 2018 | 5 | 84 | 3 | 140 | 15.0% | 2.89 [0.67, 12.42] |
| Rieger 2018 | 1 | 30 | 2 | 74 | 5.4% | 1.24 [0.11, 14.23] |
| Sessa 2018 | 14 | 151 | 3 | 49 | 19.1% | 1.57 [0.43, 5.70] |
| Tamma 2019 | 0 | 122 | 1 | 518 | 3.1% | 1.41 [0.06, 34.78] |
| Thurber 2019 | 0 | 14 | 3 | 229 | 3.5% | 2.23 [0.11, 45.29] |
| **Total (95% CI)** | | **623** | | **1489** | **100.0%** | **2.05 [1.17, 3.61]** |
| Total events | 34 | | 28 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.74$, df = 7 ($P = 0.97$); $I^2 = 0\%$

Test for overall effect: Z = 2.50 ($P = 0.01$)




- Punjabi et al. performed a meta-analysis of studies assessing oral step-down therapy for **Enterobacteriaceae bacteremia**
  - No difference in 30-day mortality
  - BUT infection recurrence at primary site or bloodstream more common in oral beta-lactam group vs. fluroquinolone/TMP-SMX (5.46% vs. 1.98%)
    - Unclear if some of this is related to suboptimal beta-lactam dosing


Sutton JD, et al. JAMA Network Open.2020;3:e2020166
Punjabi C, et al Open Forum Infect Dis. 2019;6(0):ofz364

# Impact of oral Bioavailability on GNB Therapy

- Daneman et al. studied outcomes in 2012 patients with **GNB** who were >65 years old and treated with high oral bioavailability antibiotics (TMP-SMX, quinolones) versus low oral bioavailability (beta-lactams) in a propensity score matched analysis

**Table 3**
Adjusted propensity-matched analysis of the primary and secondary outcomes among patients with gram-negative bloodstream infection treated with highly versus less-bioavailable drugs at discharge

| Outcomes | Less bioavailable, *n* (%) | Highly bioavailable, *n* (%) | p | Highly (vs. Less) bioavailable, odds ratio (95% CI) |
|---|---|---|---|---|
| 90-d outcome | | | | |
| Primary composite of mortality, recurrent BSI, or re-admission | 216 (21.5) | 171 (17.0) | 0.01 | 0.74 (0.59–0.93) |
| 90-d secondary outcomes | | | | |
| Mortality | 49 (4.9) | 43 (4.3) | 0.52 | 0.87 (0.57–1.32) |
| Recurrent BSI | 100 (9.9) | 62 (6.2) | 0.00 | 0.59 (0.42–0.82) |
| Re-admission | 141 (14.0) | 121 (12.0) | 0.19 | 0.84 (0.65–1.09) |
| ER visit | 107 (10.6) | 110 (10.9) | 0.83 | 1.03 (0.78–1.37) |
| Repeat outpatient antibiotic use | 140 (13.9) | 122 (12.1) | 0.23 | 0.86 (0.66–1.11) |
| Development of antibiotic resistance | <6[a] | <6[a] | 0.71 | 0.75 (0.17–3.35) |

- Geyer et al. studied outcomes in 194 patients with **Enterobacterales** bacteremia due to UTI treated with quinolone or TMP-SMX vs. **high dose oral cephalexin (1 g PO TID) or amoxicillin (1 g po TID)**
  - No difference in composite of mortality or recurrent bacteremia with in 30 days

Mponponsuo K, et al. Clin Microbiol Infect 2023; 23:490-497.
Geyer AC, et al. Antimicrob Steward Healthc Epidemiol 2023. doi: 10.1017/ash.2023.435

# Practical Conclusions: Oral therapy for GNB

- While studies suggest quinolones/TMP-SMX appear to perform better than oral beta-lactams for **Enterobacterales**, both groups have important toxicities
  - Limitations: Most studies left out non-**Enterobacterales** and had limited immunocompromised patients
- Reasons we don't like quinolones
  - Multiple warnings issued by FDA for risk of tendonopathy, neuropsychiatric side effects and possibly increased risk of aneurysms
  - Overuse has led to relatively frequent resistance among gram-negative organisms
  - Quinolones have been associated with increased C. diff risk in some studies
- Challenges with TMP-SMX
  - Risks include reversible impact on creatinine, hyperkalemia, abnormal LFTs and rash
- When and how to try beta-lactams
  - **When:** In cases where resistance precludes use of drugs with high oral bioavailability and IV therapy is not a reasonable option
  - **How:** With careful attention to optimized dosing….

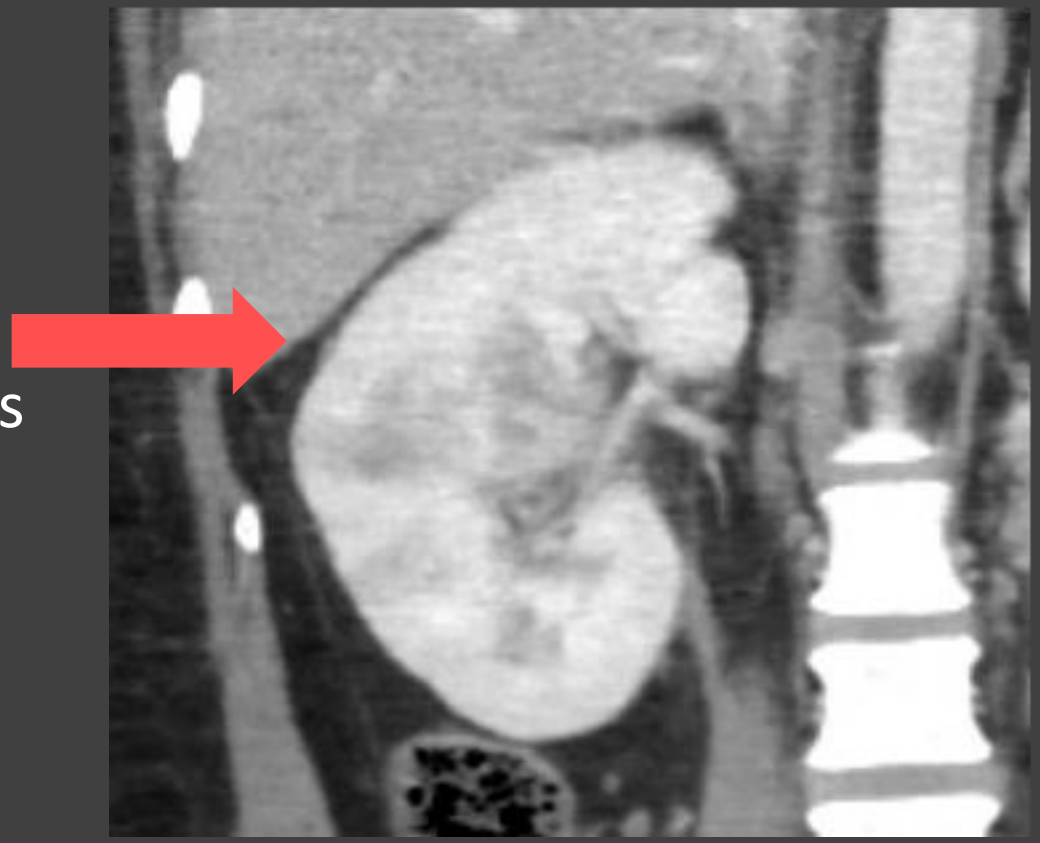
Tamma PD, et al. JAMA Intern Med 2019;179:316-23.
Punjabi C, et al Open Forum Infect Dis. 2019;6(0):ofz364

# New Approach to Old Problems:

Shorter course of antibiotics for bloodstream infection

# Similar Clinical Question– different choices

- A 35-year-old woman with obesity and recurrent UTI presents with fever to 103F, tachycardia, hypotension and right flank pain
  - CT imaging consistent with pyelonephritis
- She is admitted to the ICU where she needs pressors for 12 hours but quickly improves on empiric cefepime
- 4 of 4 **Blood cultures** and **urine culture** from admission grow **E coli**
  - Subsequent blood cultures negative
- She is afebrile and normotensive 4 days later



# What's the best antibiotic regimen for her on hospital day 4?

- Allergies: Sulfa causes throat swelling and wheezing

- E coli urine susceptibilities
  - Ampicillin resistant
  - Cefazolin resistant
  - Cefepime susceptible
  - Ceftriaxone susceptible
  - Ciprofloxacin resistant
  - Levofloxacin resistant
  - Nitrofurantoin susceptible
  - Trimethoprim-sulfamethoxazole susceptible

A. Oral cephalexin x 10 days
B. IV ceftriaxone x 3 more days
C. IV cefepime x 6 more days
D. Trimethoprim-sulfa desensitization, then give x 6 more days
E. IV cefepime x 3 more days

# A shift to shorter courses of antibiotics for bloodstream infection?

- Bloodstream infection affects over half a million people per year in North America
- Historically bloodstream infection has been treated with long courses of antibiotics (>10 days) due to concerns about recurrence
  - Optimal duration studies for organ-specific infections often exclude bacteremic patients
- However, with increasing awareness of the importance of antimicrobial stewardship several recent studies have explored the performance of short courses of antibiotics for GNB relative to longer courses

Daneman N and Fowler RA. Clin Infect Dis. 2019;69(7):1099–100.
Daneman N, et al. BMJ Open 2020;10:e038300.

| Study Details | Comparison | Outcomes | Limitations | Exclusions |
|---|---|---|---|---|
| • **Yahav et al. CID 2019**<br>• **Type:** Randomized clinical trial<br>• **Where:** 2 Israeli and 1 Italian academic medical centers<br>• **When:** 2013-2017<br>• **Patients:** **604** patients with aerobic GNB | 7d (306) **vs.** 14d (298) of antibiotics | • **Clinical failure** (all-cause mortality at 90d, relapse, suppurative, or distant complications; readmission or extended hospitalization) **was similar in the two groups**: 45.8% in 7d vs 48.3% in 14d group (risk difference, –2.6% [95% CI –10.5% to 5.3%]) | • Treatment assignment not blinded<br>• 68% of patients had urinary source<br>• ~10% of patients had non enteric GNB | • Hemodynamic instability of fever w/in 48 hours<br>• Uncontrolled focus of infection<br>• Immunosuppression<br>• Polymicrobial GNB |
| • **Von Dach et al. JAMA 2020**<br>• **Type:** Partially–blinded randomized clinical trial<br>• **Where:** 3 Swiss tertiary care hospitals<br>• **When:** 2017-2019<br>• **Patients:** **504** Adults with GNB | CRP-guided antibiotic duration* (170) **vs.** 7d antibiotics (169) **vs**. 14d antibiotics (165) | • 2.4% in the CRP arm vs. 6.6% in the 7d arm vs. 5.5% in the 14d arm had *clinical failure* (defined as: recurrent GNB, local or distant bacterial complication, restart of antibacterials, 30d mortality)<br>• **Both CRP-guided and 7d arm were non-inferior to 14d arm** | • Low rate of clinical failure limits interpretation<br>• 69% of patients had urinary source<br>• 75% of bacteremias were *E coli* | • Hemodynamic instability or fever w/in 24 hours<br>• Immunosuppression<br>• Recurrent, non-fermenting GNB or polymicrobial bacteremia |
| • **Molina et al. CMI 2022**<br>• **Type:** Randomized clinical trial<br>• **Where:** 5 Spanish medical centers<br>• **When:** 2014-2016<br>• **Patients:** **248** Adults with *Enterobacterales* bacteremia | 7d (119) vs. 14d (129) of antibiotics | • **Primary endpoint:** total number of antibiotic days from positive blood culture to day 28→ median was 7 (7-14) in 7d arm vs. 14 (14-16) I 14d arm<br>• There was no difference in clinical outcomes including mortality, relapse of bacteremia, relapse of fever or drug-related adverse events | • Treatment assignment not blinded<br>• ~60% of isolates E coli<br>• 55% related to UTI<br>• Endpoint (antibiotics days) close to intervention | • Uncontrolled bacteremia<br>• Neutropenia anticipated for >7d<br>• Infection that requires prolonged treatment<br>• Carbapenemase-producing organism |

*CRP arm stopped antibiotics when CRP 75% reduced from peak

# BALANCE (Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness) Trial 2024

- Multicenter open-label randomized trial that compared 7 vs 14 days of antibiotics to treat bacteremia in **3608** hospitalized patients
  - **Important details**
    - **A**ntibiotic choice, dose & delivery mode up to investigator
    - Investigators blinded to the arm of treatment **until day 7**
  - **Important exclusions**
    - Immunocompromise (solid organ or stem cell transplant, neutropenia)
    - Prosthetic heart valve
    - Endovascular graft
    - Suspected syndrome that requires long treatment (e.g. osteomyelitis)
    - Suspected contaminant blood culture
    - Staph aureus bacteremia
    - Fungemia
- Primary outcome was death from any cause at 90 days after bacteremia

Daneman N, et al. N Engl J Med 2025;392:1065-78

# Balance Trial Results

- Key characteristics were balanced between arms:
  - Level of illness: 55% in ICU, 45% on hospital ward, 22% on mech ventilation
  - Comorbidities: 32% diabetes, 22% solid tumor cancer
  - Bacteremia source: 42% urinary, 19% GI or biliary, 13% pulmonary

| Most commonly isolated pathogens in blood cultures — no. (%)‖ | |
|---|---|
| *Escherichia coli* | 1582 (43.8) |
| Klebsiella species | 552 (15.3) |
| Enterococcus species | 250 (6.9) |
| Coagulase-negative staphylococci | 174 (4.8) |
| Pseudomonas species | 170 (4.7) |

Daneman N, et al. N Engl J Med 2025;392:1065-78

**Table 2. Primary and Secondary Outcomes.**

| Outcome | 7-Day Group (N=1814) | 14-Day Group (N=1794) | Difference (95% CI)* |
|---|---|---|---|
| | | | *percentage points* |
| **Primary outcome, death from any cause by 90 days — no./total no. (%)** | | | |
| Primary analysis, intention-to-treat population | 261/1802 (14.5) | 286/1779 (16.1) | −1.6 (−4.0 to 0.8) |
| Secondary analysis, per-protocol population | 178/1370 (13.0) | 222/1483 (15.0) | −2.0 (−4.5 to 0.6) |
| Modified intention-to-treat analysis, survival ≥7 days | 247/1788 (13.8) | 272/1765 (15.4) | −1.6 (−3.9 to 0.7) |
| **Secondary outcomes** | | | |
| Death in hospital — no. (%)† | 168 (9.3) | 184 (10.3) | −1.0 (−2.9 to 0.9) |
| Death in ICU — no./total no. (%)‡ | 91/1014 (9.0) | 97/1008 (9.6) | −0.6 (−3.2 to 1.9) |
| Median no. of days in hospital (IQR) | 10 (6–21) | 11 (6–22) | −1 (−1.5 to −0.5) |
| Median no. of hospital-free days by day 28 (IQR) | 17 (0–21) | 15 (0–21) | 2 (0.8 to 3.2) |
| Median no. of days in ICU (IQR)§ | 5 (3–11) | 5 (3–11) | 0 (−0.4 to 0.4) |
| Median no. of days of vasopressor use (IQR) ¶ | 3 (2–5) | 3 (2–4) | 0 |
| Median no. of days of mechanical ventilation (IQR)‖ | 6 (3–14) | 5 (2–12) | 1 (−0.6 to 2.6) |
| Relapse of bacteremia — no. (%) | 47 (2.6) | 39 (2.2) | 0.4 (−0.6 to 1.4) |
| Median no. of antibiotic-free days by day 28 (IQR)** | 19 (11–21) | 14 (11–14) | 5 (4.6 to 5.4) |
| Antimicrobial-related adverse outcomes — no. (%) | | | |
| Allergy | 14 (0.8) | 19 (1.1) | −0.3 (−0.9 to 0.3) |
| Anaphylaxis | 1 (0.1) | 1 (0.1) | 0 (−0.2 to 0.2) |
| Acute kidney injury | 15 (0.8) | 17 (0.9) | −0.1 (−0.7 to 0.5) |
| Acute hepatitis | 2 (0.1) | 4 (0.2) | −0.1 (−0.4 to 0.2) |
| *Clostridioides difficile* infection — no. (%) | 31 (1.7) | 35 (2.0) | −0.2 (−1.1 to 0.6) |
| Secondary infection or colonization with antibiotic-resistant organisms — no. (%) | 173 (9.5) | 152 (8.5) | 1.1 (−0.8 to 2.9) |
| Secondary infection or colonization with antibiotic-resistant organisms in sterile culture — no. (%) | 20 (1.1) | 24 (1.3) | −0.2 (−1 to 0.5) |

# Practical Conclusions: How long to treat bacteremia?

- Recent studies show that 7 days of antibiotics are likely equally as effective as 14 days to treat bacteremia *in the right patient population*
  - Studies largely excluded  several specific issues including
    - Patients with complicated infection (e.g. undrained abscess, osteomyelitis, endocarditis)
    - Certain types of bacteria→ Pseudomonas and non-fermenters excluded or underrepresented
      - Only BALANCE trial assessed gram positive organisms, but excluded Staph aureus and Staph lugdunensis
    - Certain types of hosts → transplant and neutropenic patients largely excluded
  - Data suggest this may be safe for critically ill patients→ Balance trial did include ICU patients

Von Dach E, et al. JAMA. 2020;323:2160-9.
Yahav D, et al. Clin Infect Dis 2019; 69:1091–8.
Molina J, et al. Clin Microbiol Infect 2022;28:550-7.
Daneman N, et al. N Engl J Med 2025;392:1065-78.

# New Problems:

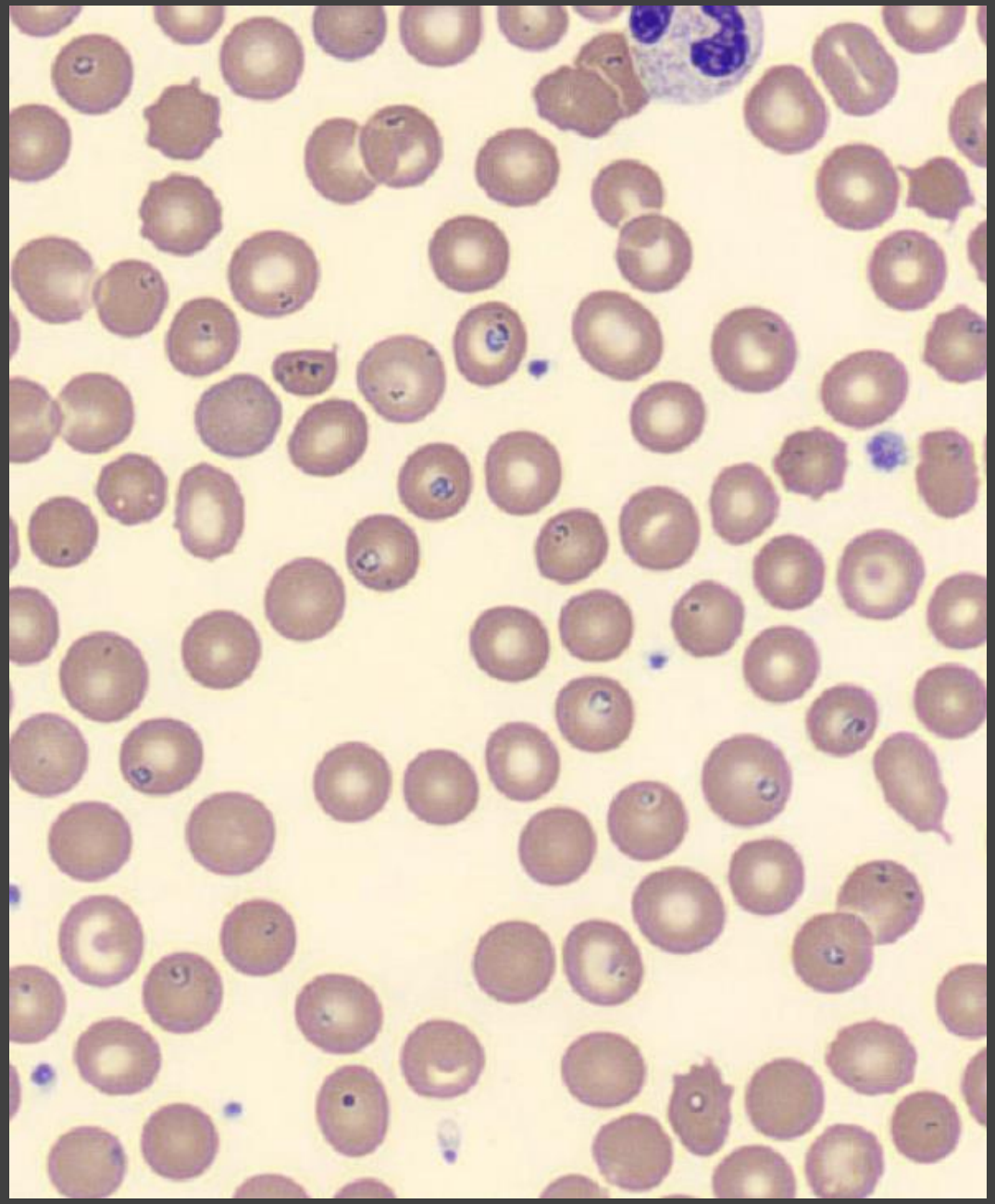
Impact of climate change on infection

# Clinical Case

- 68-year-old man with diffuse large B cell lymphoma s/p 6 cycles of R-CHOP chemotherapy 4 months ago presents the first week of January with malaise, dyspnea on exertion and sweats that have progressed for the last 2 weeks
  - His daughter notes that he looks yellow
- Past medical history is notable for lymphoma as above, hypertension, hyperlipidemia and asplenia (MVA at age 18)
- Medications include atorvastatin, amlodipine and lisonopril
- Social history is notable for living in the suburbs of Boston. Retired engineer.  Two pet Labradors that he walks in a nearby nature reserve daily. Just returned from a holiday vacation to Hawaii for 10 days.

# Examination & Labs

- Exam
  - Notable for a fatigued appearing man with pale conjunctiva
  - Mild tachycardia with regular rhythm
  - Clear lungs but is tachypneic
- Labs
  - WBC 4.2, HCT 24, PLT 301
    - Differential sent…
  - Cr 1.4, AST 111, ALT 34, T Bili 2.9
  - LDH 1102



# The likely cause of his illness is:

A. Malaria
B. Leptospirosis
C. Babesia
D. Oroyo fever (Bartonella bacilifomis)
E. Dengue fever

# Climate change and Infection

- Climate change has the potential to have broad reaching impacts on human infection
- Knowledge of some changes we see now can help with prevention and early diagnosis

Table. Impact of Climate-Related Changes on Infectious Disease Epidemiology

| Disease type | Climate-related change | Effect on infectious disease epidemiology | Examples |
|---|---|---|---|
| Vector-borne diseases | Shorter, warmer winters<br>Longer summers<br>Expanding range of vectors, eg, mosquitoes and ticks<br>Changes in precipitation patterns | Increased disease incidence<br>Expanding seasonality into winter months<br>Expanding geographic range, primarily northward and westward<br>Increased likelihood of onward transmission | Babesiosis<br>Lyme disease<br>Anaplasmosis<br>Powassan virus<br>Ehrlichiosis<br>Dengue<br>Zika virus<br>Chikungunya virus<br>Malaria |
| Zoonotic diseases | Changes in animal migration patterns, natural ranges, and population density<br>Habitat destruction<br>Increased interaction between different animal species<br>Increased human-animal interaction | Increased cross-species transmission events<br>Emergence of novel human pathogens<br>Increased disease incidence<br>Expanding geographic range | Avian influenza (H5N1)<br>Plague<br>Hantavirus<br>Tularemia<br>Emerging coronaviruses |
| Fungal diseases | Expanded thermotolerance in fungal organisms<br>New favorable environments for endemic fungi | Emergence of novel human pathogens<br>Expanding geographic range of endemic mycoses | *Candida auris*<br>*Sporothrix brasiliensis*<br>*Coccidioides*<br>*Histoplasma*<br>*Blastomyces* |
| Waterborne diseases | Rise of sea level<br>Extreme weather events<br>Flooding-induced strain on water infrastructure<br>Changes in precipitation patterns<br>Changes in coastal water temperature | Increased disease incidence after storms<br>Expanding seasonality<br>Expanding geographic range, primarily northward | *Campylobacter*<br>*Escherichia coli*<br>*Cryptosporidium*<br>*Vibrio* species |

Phillips MC, LaRocque RC, Thompson GR. JAMA 2024; doi: 10.1001/jama.2023.27724

# How might climate change impact fungal infection?

- Humans have two major defenses against invasive fungal infection:
  1. Relatively high body temperature (we're warm-blooded!)
  2. Immune defenses
- Warm ambient temperatures and particularly the number of days with excessive heat can select for environmental fungi that rapidly adapt to survive at warmer temperatures
  - Fungi that survive at warmer temperatures can be better suited to cause human infection
  - The first potential example of this: *Candida auris*, which has significant thermotolerance (grows well at 37°C), emerged on different continents ~2010
    - This organism can cause difficult-to-treat infection in a vulnerable population (ICU in particular) and is typically multidrug resistant
  - Other fungi not known to cause human infection now could adapt and cause new syndromes

Casadevall A. Nat Microbiol. 2023;8:2217-2219.
Seidel D, et al. Lancet Microbe. 2024; doi.10.1016/S2666-5247(24)00039-9

# Climate change & Fungi: Distribution & Disasters

- Distribution
  - The distribution of endemic mycoses i
  - Modeling studies have suggested that the Ohio river valley has expanded to
  - Modelling studies have also suggested the Northwest US
- Increased natural disasters m[illegible] lea difficult invasive fungal i[illegible]ction

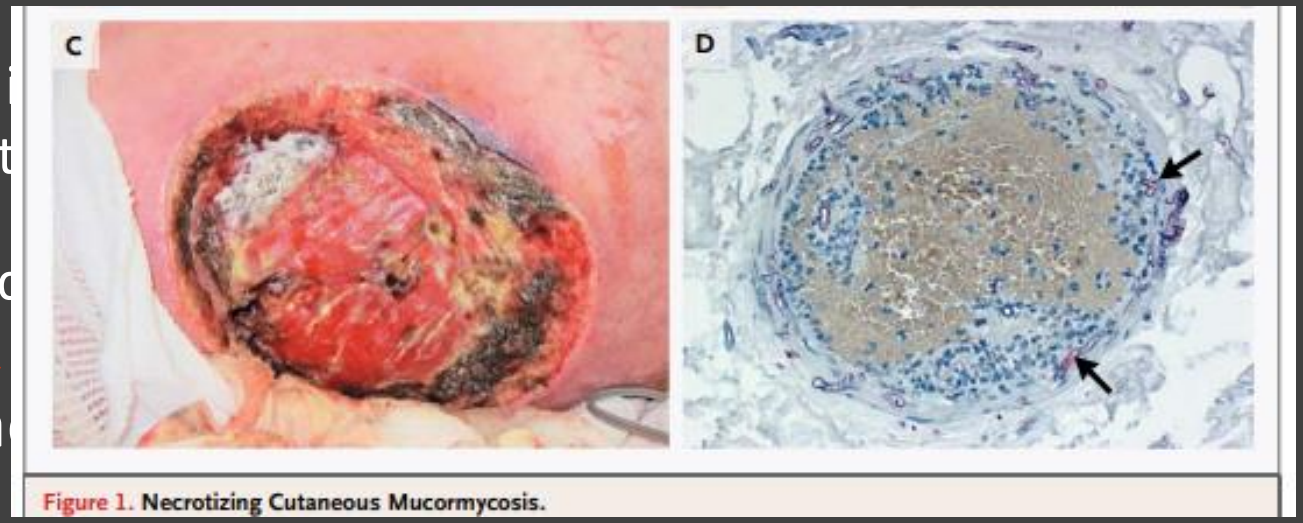


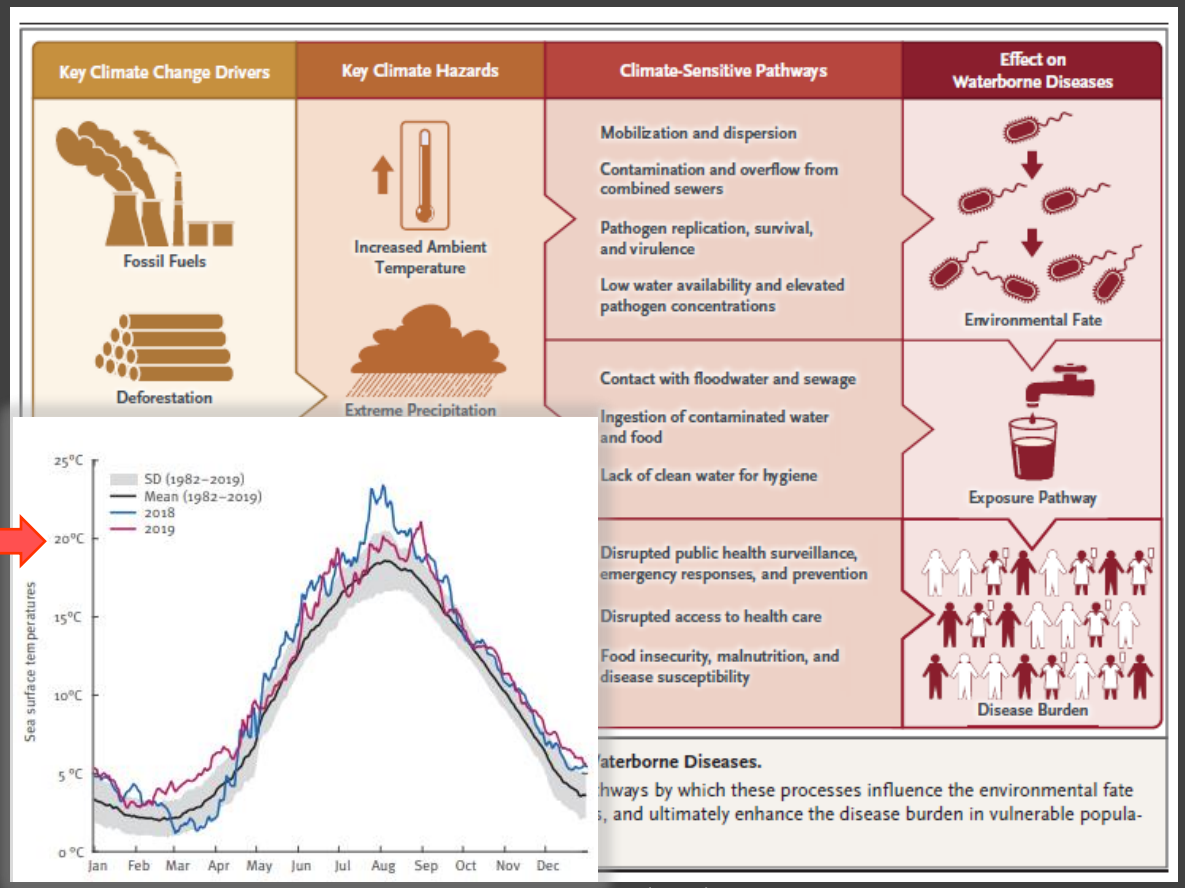
Figure 1. Necrotizing Cutaneous Mucormycosis.

  - **Tornado eg:** Joplin, Missouri 2011: following a severe tornado (winds >200 miles per hour) a cluster of cutaneous mucormycosis was reported in 13 injured individuals due to *Apophysomyces trapeziformis*
  - **Wildfire eg:** Wildfire smoke contains microbes including fungal spores
    - Mulliken et al. studied the association between wildfire smoke and California hospital admissions for Coccidioides and Aspergillus and found that Coccidioides admissions rose 20% in the month following smoke exposure based on smoke plume data

Seidel D, et al. Lancet Microbe. 2024; doi.10.1016/S2666-5247(24)00039-9.
Fanfair RN, et al. N Engl J Med 2012;367:2214-25.
Mulliken JS, et al. Lancet Planet Health 2023; 7: e381–86

# Waterborne Infection and Climate Change

- Climate change has impacted movement of water between earth & atmosphere
  - Increased evaporation has increased atmospheric water vapor
- This can favor certain waterborne pathogens:
  - Some thrive with increased flooding or sea level surges due to dispersion and contamination (fecal pathogens, leptospirosis)
  - Some thrive in warmer water directly (Salmonella, vibrio, amoeba) or indirectly (Legionella in air conditioning units)
- Eg: Vibrio infection has increased globally
  - Outbreak of domestically acquired infections in Germany in 2018-2019 associated with increased temperatures in Baltic Sea
  - In Maryland there was 39% increase in average Vibrio infection incidence from 2006-12 vs. 2013-19
    - Same research group showed linear relationship between water temperature and V. vulnificus presence in Chesapeake








Semenza JC, Ko AI. N Engl J Med2023;389:2175-87
Brehm TT et al. Euro Surveill 2021; doi: 10.2807/1560-7917.ES.2021.26.41.2002041
Brumfield KD et al. Appl Environ Microbiol. 2023; doi: 10.1128/aem.00307-23
Morgado ME, et al. Environ Res 2024; doi: 10.1016/j.envres.2023.117940.

# Summary thoughts on climate and infection

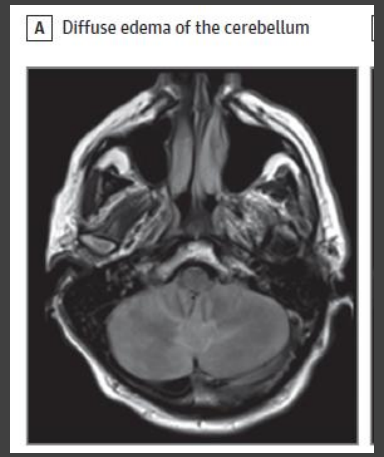
- How does it help us to understand how climate change may impact infectious diseases risk?
  - Climate change literature can feel heavy and leave providers feeling helpless
  - However, regardless of one's stance on climate change, knowledge is helpful!
    - Natural disasters can be associated with increased waterborne and invasive fungal infection so knowledge can lead to earlier diagnosis and better outcomes
    - Travel advice with awareness of shifting epidemiology (e.g. increased vibrio risk in areas previously with cooler water) can be helpful for infection prevention and earlier recognition of infection
      - This includes checking available public health resources about infection risk in certain locations even domestically

# Formidable New & Old Bugs:

Powassan

# Clinical Case Description

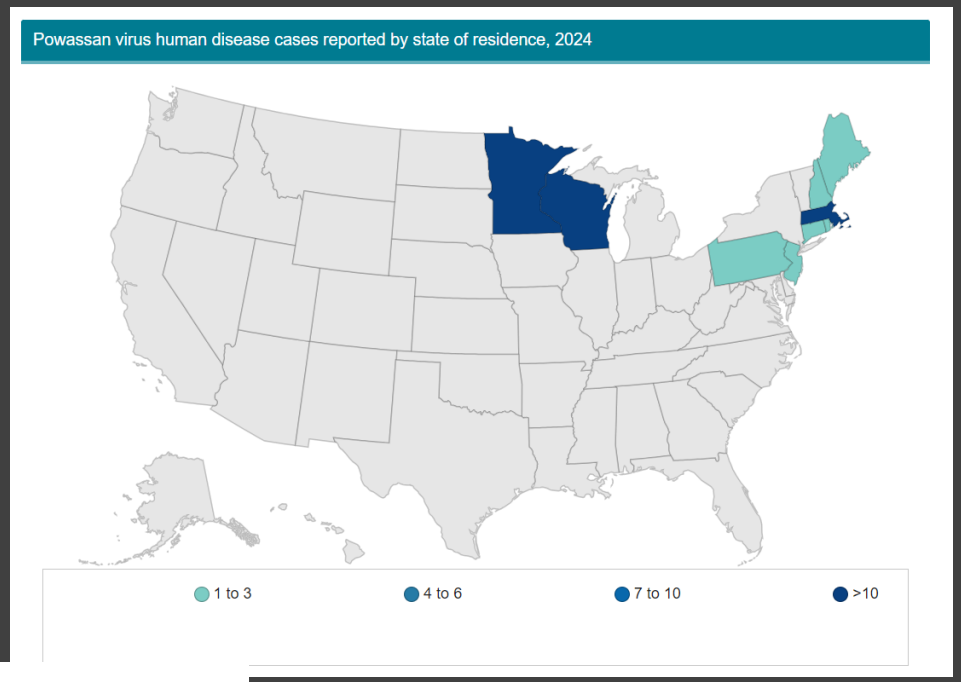
- 82-year-old man with hypertension and CAD from Boston suburbs presents in July with 3-4 days of fever, nausea, anorexia and diarrhea
  - He was evaluated at a local ED where he was treated with IV fluids and diagnosed with gastroenteritis
- Three days later he developed dysarthria, diplopia and gait instability that led him to re-presented
  - Lumbar puncture showed 40 nucleated cells (82% lymphocytes), total protein 69 g/dL, glucose was normal
  - He was treated with empiric broad spectrum antimicrobials
- Brain MRI demonstrated rhombencephalitis
- Serum and CSF testing for Powassan IgM positive

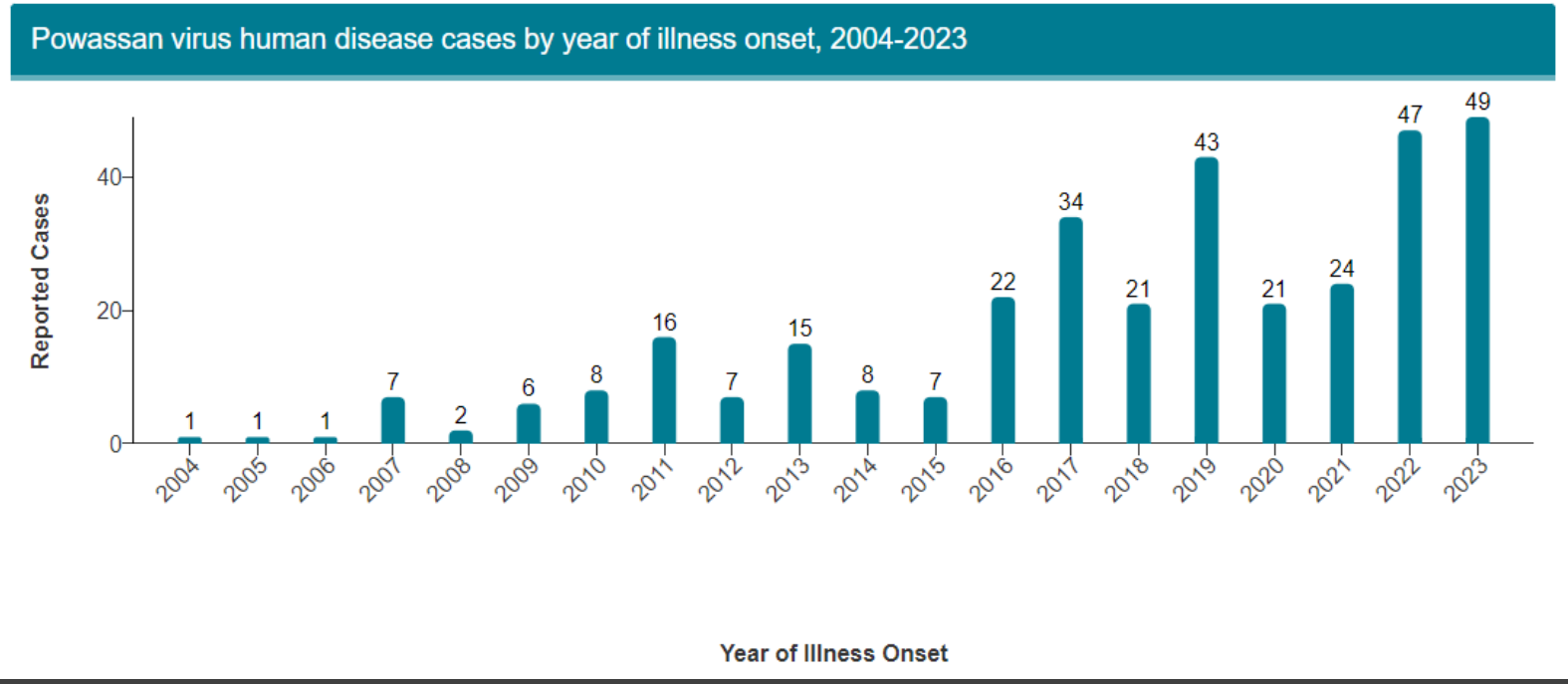


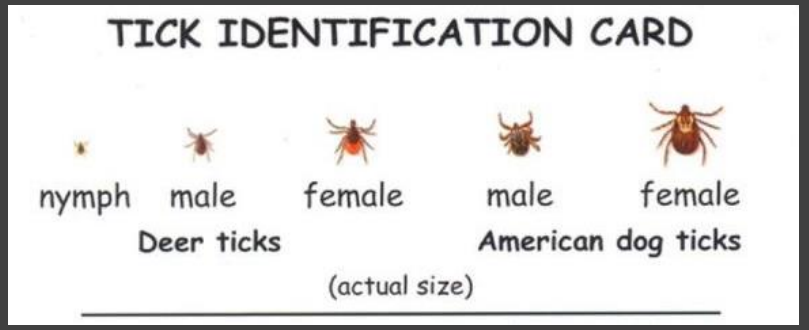

Solomon IH, et al. JAMA Neurol. 2018;75:746-50.

# Powassan

- Flavivirus carried by Ixodes scapularis (and Ix. cookei, Ix. marxi)
  - Frequency of detection in animal hosts increasing
  - Frequency of reported cases in the Northeast has been increasing in the last 10 years
- Duration of tick exposure needed to acquire infection is short—15 minutes
- Incubation period is 1-5 weeks





https://www.cdc.gov/powassan/data-maps/current-year-data.html
https://www.cdc.gov/powassan/data-maps/historic-data.html
https://www.mass.gov/doc/tick-borne-educational-materials-tick-identification-card/download
Piantadosi A , Solomon I. Infect Dis Clin N Am 2022;671-88.
Piantadosi A, et al. Clin Infect Dis 2016;62:707–13.

# Powassan: Clinical Characteristics

- Prevalence of mild infection is unknown—suspected to be more common than neuroinvasive disease
  - Testing likely heavily biased in patients with neuroinvasive disease and large seroprevalence studies are lacking
- Piantadosi, et al. reported 8 cases in MA & NH 2013-15
  - Most previously healthy with known tick exposure presenting with headaches, fevers and altered mental status
- Mendoza, et al. reported 16 cases in MN & WI 2013-22 at Mayo and described clinical presentation
- There is no antiviral therapy, but IVIg has been tried in some patients
  - Death reported in 10-19% and longer term neurological sequalae common in survivors

| Characteristic | Patients, No. (%)[a] (n = 16) |
|---|---|
| Age, median (IQR) y | 63.2 (48.2–74.6) |
| Age range | 1.6 mo to 78 y |
| Male sex | 10 (62.5) |
| Immunosuppression | 4 (25) |
| Symptoms at presentation | |
| Fever | 15 (93.8) |
| Rash | 4 (25) |
| Headache | 8 (50) |
| Altered mental status | 9 (56.3) |
| Neurologic phenotype | |
| Rhombencephalitis | 6 (37.5) |
| Meningoencephalitis | 3 (18.8) |
| Meningitis | 4 (25) |
| Meningoencephalomyelitis | 2 (12.5) |
| OMS | 1 (6.3) |
| Laboratory results at admission, median (IQR) | |
| Hemoglobin, g/dL | 12.4 (12.2–13.7) |
| WBC count, $\times 10^9$ cells/L | 10.9 (7.6–12.3) |
| Absolute neutrophil count, $\times 10^9$ cell/L | 8.0 (5.8–9.7) |
| Absolute lymphocyte count, $\times 10^9$ cells/L | 1.27 (0.9–1.8) |
| Platelets, $\times 10^9$ cells/L | 162 (136.8–189.8)[b] |
| Creatinine, mg/dL | 1.09 (0.8–1.4) |
| ALT, mg/dL | 24.5 (18.8–35.8) |
| AST, mg/dL | 30 (23.0–41.3) |
| Total bilirubin, mg/dL | 0.6 (0.4–0.7) |
| CSF results, median (IQR) (n = 15) | |
| Protein, mg/dL | 79 (70.5–100.5)[c] |
| Glucose, mg/dL | 58 (52–67) |
| Glucose/serum ratio | 0.6 (0.5–0.6) |
| Nucleated cells, cells/μL | 121 (49–265.5)[c] |
| Neutrophils, cells/μL | 11.72 (3.6–17.6) |
| Lymphocytes, cells/μL | 58 (27.8–205.8) |
| Monocytes, cells/μL | 10.73 (3.08–25.33) |
| MR imaging results (n = 15) | |
| Normal | 7 (46.7) |
| Cerebellitis | 3 (20) |
| Leptomeningeal enhancement | 5 (33.3) |
| Basal ganglia involvement | 2 (13.3) |

Piantadosi A and Solomon I. Infect Dis Clin N Am 2022;671-88.
Piantadosi A, et al. Clin Infect Dis 2016;62:707–13.
Mendoza MA, et al. Clin Infect Dis. 2024;78:80–9

# Summary

- **Oral antibiotics for GNB**
  - Oral antibiotics with high bioavailability like quinolones and TMP-SMX perform as well as IV antibiotics for GNB but have important toxicities
  - Risk of worse outcome may be higher with oral beta lactams
- **Shorter course of antibiotics for bacteremia**
  - 7 days of antibiotics may work as well as 14 days for bacteremia therapy
  - Role of short course antibiotics is less clear in certain populations and with gram positive infections
- **Climate change:**
  - Climate change is impacting human infection risk through changes in vector-borne, zoonotic, fungal and water-borne infection patterns
  - Knowledge of changes can help with improved diagnosis and avoidance
- Powassan
  - Viral infection transmitted by even brief deer tick bites in endemic areas with potential to cause serious neurological morbidity and mortality

# Disclosures

- I have research funding from Cidara, Mundipharma, F2G, Scynexis and GSK
- I have been a consultant for Melinta, Pfizer, Roche, Seres therapeutics, Takeda and Treeline biosciences

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