Hot Topics in Infectious Diseases

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Global and Continuing Education

Disclosures

- I have research funding from Merck, F2G, Scynexis and GSK
- I have been a consultant for biointelect (past) and F2G (current)

What's New in Infectious Diseases?

- Formidable New & Old Bugs
  - COVID-19 and all its variants
  - Multi-drug resistant organisms
  - *Burkholderia pseudomallei*
- New Antimicrobials
  - Cefiderocol 2019
  - Imipenem-relebactam 2019
  - Lefamulin 2019
  - Remdesivir 2020
  - Ibrexafungerp 2021
- New Approach to Old Problems
  - Oral antibiotics for serious invasive infection
  - Shorter antimicrobial courses for bloodstream infection
- New Guidelines for Screening and Therapy
  - Antimicrobial resistance 2022
  - C. difficile 2021
  - Lyme disease and babesia 2020
  - Asymptomatic bacteriuria 2019
- New Diagnostic Tools
  - Next generation sequencing

Learning Objectives

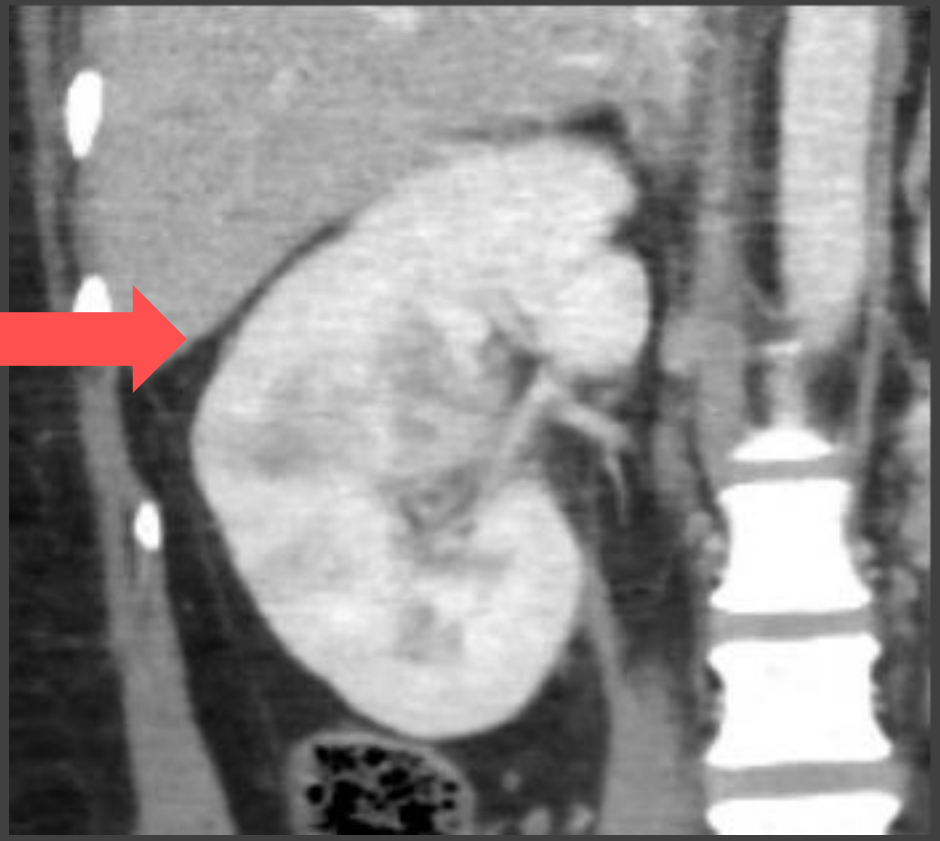
- Learn when enteric gram-negative bloodstream infections might be managed with oral antimicrobials or short (<10 days) courses of antibiotics
- Learn the many instances where screening for urinary tract infection/bacteriuria should *not* be performed routinely
- Learn up-to-date testing algorithms for Lyme disease and how to manage concerns about Lyme exposure by tick bites

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 resistant
  - Cefepime susceptible
  - Ceftriaxone susceptible
  - Ciprofloxacin resistant
  - Levofloxacin resistant
  - Nitrofurantoin susceptible
  - Trimethoprim-sulfamethoxazole susceptible

A. Oral nitrofurantoin x5 days
B. IV ceftriaxone x 10 days
C. Oral trimethoprim-sulfa x 10 days
D. Oral cephalexin x7 days
E. Oral cefpodoxime 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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  2. Endocarditis
  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 infectious disease study and debate!

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

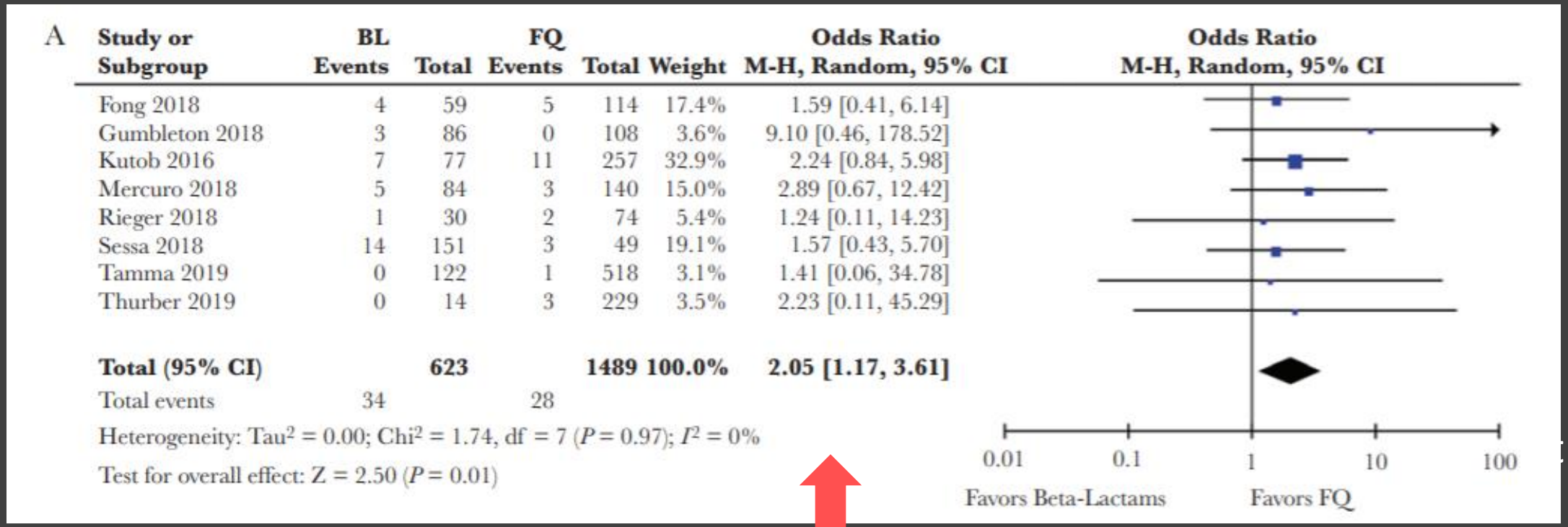
- Certain antibiotics have excellent oral bioavailability such that oral therapy achieves similar concentrations to IV (eg. levofloxacin)
  - In some cases where oral bioavailability is less, increased dose of oral agent can overcome lower bioavailability (eg. Ciprofloxacin→ 400 IV = 750mg po)
  - In 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 GNB and **adequate source control**
  - GNB sources: Urinary tract (40%), GI tract (20%) catheter-associated (18%), pulmonary (4%), SSTI (3%)
- 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
  - The low number of patients treated with low bioavailability oral antibiotics limited statistical power to address the importance of bioavailability

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



- Punjabi et al. performed a meta-analysis of studies assessing oral step-down therapy for GNB
  - 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

Practical Conclusions: Oral GNB therapy in whom?

- Who is the right patient with GNB in whom to consider step-down to oral therapy?
  - Studies assessing oral stepdown therapy were largely limited to uncomplicated episodes of GNB
- There are no guidelines, but Heil et al. compiled an expert panel to arrive at a consensus guidance statement by the Delphi method

Patients with uncomplicated gram-negative bloodstream infections can be treated with oral antibiotics if all of the following criteria are all met:
a. Clinical improvement observed on effective intravenous therapy
i. If effective oral therapy was started initially and appropriate clinical response is achieved, oral therapy can continue for the duration of the treatment course
b. Underlying source is confirmed
c. Susceptibility testing confirms that oral antibiotic options are available
d. The patient has an intact and functional gastrointestinal tract

Heil EL, Open Forum Infect Dis. 2021;8: ofab434

Practical Conclusions: Which Oral GNB therapy ?

- While studies suggest quinolones/TMP-SMX may perform better than oral beta-lactams for GNB, both groups have important toxicities
- 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. difficile risk
- 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
    - E.g. recent study compared ertapenem to novel oral carbapenem for complicated UTI with positive results
  - **How:** With careful attention to optimized dosing….

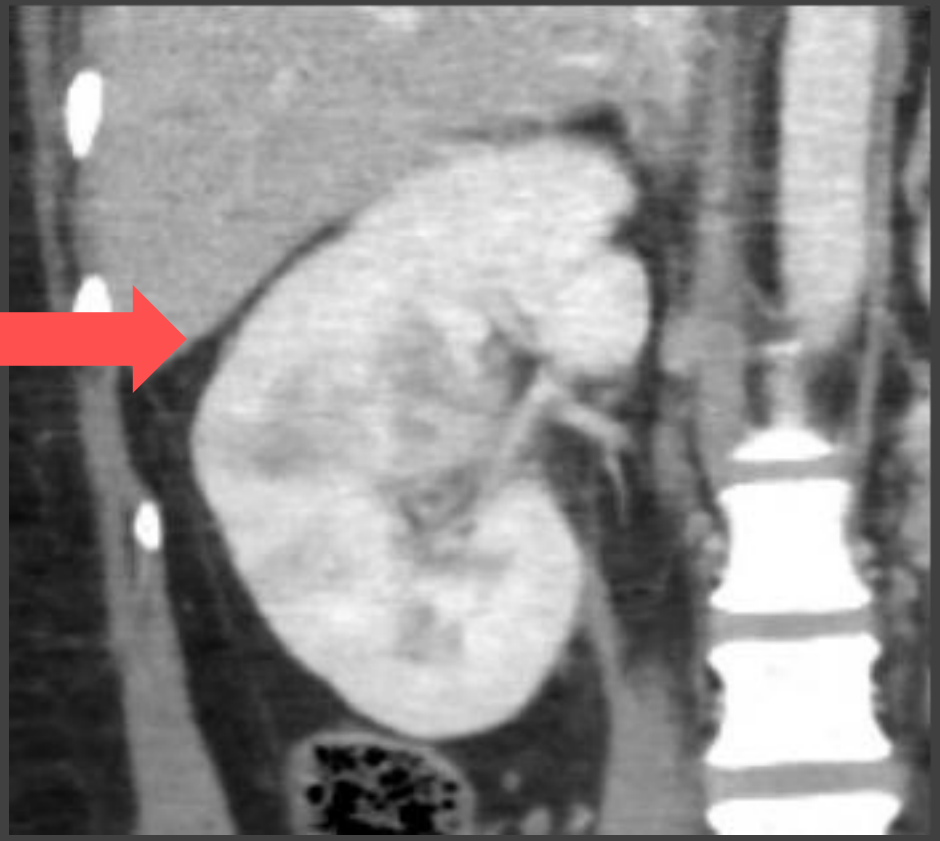
Tamma PD, et al. JAMA Intern Med 2019;179:316-23.
Punjabi C, et al Open Forum Infect Dis. 2019;6(0):ofz364
PB Eckburg et a, N Engl J Med. 2022; 386:1327-1338

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 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 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 10 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
  - There is also a large international clinical trial on going (Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness = BALANCE trial)

Daneman N and Fowler RA. Clin Infect Dis. 2019;69(7):1099–100.
https://clinicaltrials.gov/ct2/show/NCT03005145; accessed 4/27/2022

Study Details	Comparison	Outcomes	Limitations	Exclusions
• **Chotiprasitsakul et al. CID 2018** • **Type:** Observational, propensity-matched study • **Where:** 3 US academic medical centers • **When:** 2008-14 • **Patients:** 770 Adults with Enterobacteriaceae GNB	'Short' (6-10 days, 385) **vs.** 'Long' (11-16 days, 385) duration of antibiotics	• **There was no difference in 30-day mortality between the short and long treatment groups** (adjusted hazard ratio 1.00; 95% CI 0.62–1.63) • The odds of C. diff infection or recurrent bacteremia were also similar	• Though propensity score matched, it is *observational* • Patients included largely had source control– uncomplicated	• Transplant recipients • Polymicrobial bacteremia • Those who died during antibiotic therapy
• **Yahav et al. CID 2019** • **Type:** Randomized clinical trial • **Where:** 2 Israeli and 1 Italian academic medical centers • **When:** 2013-2017 • **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 • 68% of patients had urinary source • ~10% of patients had non enteric GNB	• Hemodynamic instability of fever w/in 48 hours • Uncontrolled focus of infection • Immunosuppression • Polymicrobial GNB
• **Von Dach et al. JAMA 2020** • **Type:** Partially–blinded randomized clinical trial • **Where:** 3 Swiss tertiary care hospitals • **When:** 2017-2019 • **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) • **Both CRP-guided and 7d arm were non-inferior to 14d arm**	• Low rate of clinical failure limits interpretation • 69% of patients had urinary source • 75% of bacteremias were *E coli*	• Hemodynamic instability or fever w/in 24 hours • Immunosuppression • Recurrent, non-fermenting GNB or polymicrobial bacteremia

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

Practical Conclusions: How long to treat GNB?

- Recent studies show that short courses of antibiotics (7-10 days) can be effective *in the right patient population*
  - Studies largely excluded patients with complicated infection or immunocompromise

Table 1. Consensus Statements for Best Practices for the Management of Uncomplicated Gram-Negative Bloodstream Infections

Statement	Rating[a]
1. Uncomplicated gram-negative bloodstream infections are defined as the following (the panel suggests all 4 conditions must be met):	10 strongly agree 3 agree
a. Bloodstream infection confirmed to be secondary to 1 of the following sources:	
i. Urinary tract infection	
ii. Intra-abdominal or biliary infections	
iii. Catheter-related bloodstream infection	
iv. Pneumonia (without structural lung disease, empyema/abscess, cystic fibrosis)	
v. Skin and soft tissue infection	
b. Source control (ie, removal of any infected hardware, catheters, or devices and near complete drainage of infected fluid collections, as well as imaging assurance [as needed] of no residual or metastatic sites of infection)	
c. Patients *without* immunocompromise and risk for opportunistic infections (eg, recent solid organ transplant recipients; expected prolonged neutropenia with ANC <500 cells/mL during the GN-BSI treatment course; recent CD4 cell count <200 cells/mL; chronic corticosteroids and/or immunomodulator therapy); select immunocompromised patients such as those on stable immunomodulatory therapy may be considered on a case-by-case basis	
d. Clinical improvement within 72 hours of effective antibiotic treatment—at a minimum includes defervescence and hemodynamic stability[b]	
2. Patients with uncomplicated gram-negative bloodstream infections, regardless of the gram-negative organism or resistance phenotype, can generally be treated with a 7-day course of effective therapy	9 strongly agree 4 agree

Chotiprasitsakul D et al. Clin Infect Dis 2018; 66:172–7
Von Dach E, et al. JAMA. 2020;323:2160-9.
Yahav D, et al. Clin Infect Dis 2019; 69:1091–8.
Heil EL, Open Forum Infect Dis. 2021;8: ofab434

New Guidelines

Asymptomatic Bacteriuria

Clinical Case

- 88-year-old woman with osteopenia, hypertension, and GERD is brought to the ED from her assisted living facility with right wrist swelling
  - She reports slipping on some damp leaves and falling on her hand earlier in the day while on her regular 2 mile walk around the neighborhood
  - Other than wrist pain and swelling she denies other symptoms including fevers, chills, cough, nausea, diarrhea, or dysuria
- Labs are at baseline; UA shows trace leukocyte esterase & nitrites
- X-ray of the right forearm demonstrates fracture of the right distal radius

In addition to consulting orthopedics regarding her fracture the best next step is:

A. Treat with nitrofurantoin for UTI indicated by leukocytes in urine
B. Treat with ciprofloxacin for UTI indicated by nitrites in urine
C. Since she has no UTI symptoms no further work up indicated
D. Send urine for reflex culture since occult UTI may have been the cause of her fall

Asymptomatic bacteriuria (ASB)

- Definition
  - “The presence of 1 or more species of bacteria growing in the urine at specified quantitative counts (≥105 colony-forming units [CFU]/mL or ≥108 CFU/L), irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to urinary tract infection (UTI)”
- New guidelines help clarify (1) in whom urine culture should be checked in absence of symptoms and (2) who should be treated
  - Does not include recommendations on candiduria
- Positive urine cultures often lead to treatment regardless of symptoms…
- Why should I care about judicious treatment of ASB?
  - Antimicrobial stewardship (avoid contributing to emerging resistance!)
  - Avoid antibiotic toxicities (particularly important with quinolones…)
  - Avoid ‘collateral damage’ to microbiota and C. diff

Nicolle LE , et al. Clin Infect Dis 2019; 68:e83–e110.
FDA Drug Safety Communication. https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm; accessed 4/23/2022
Gupta K, et al. Clin Infect Dis 2011;52:e103-e120.

Patient Group	Recommendations	Comments
Healthy non-pregnant pre- & post-menopausal women	**No screening or treatment**, strong, low quality	Women with ASB develop symptomatic UTI more often, but treating ASB does not reduce this risk or improve outcome
Functionally-impaired community dwelling older men & women	**No screening or treatment**, strong, low quality	Look for other sources in those with bacteriuria and **delirium or after a fall** in absence of GU or systemic infection symptoms
Long term care facility dwelling older men & women	**No screening or treatment**, strong, moderate quality	ASB linked to antibiotic treatment, but no reduction in mortality, change in mental status or admission for UTI; multidrug resistant pathogens more common
Diabetic patients	**No screening or treatment**, strong, moderate quality	In a placebo-controlled study of antibiotic treatment of women with ASB and diabetes, no difference in pyelonephritis or symptomatic UTI
Spinal cord injury with impaired void	**No screening or treatment**, strong, low quality	Caveat: *Clinical signs and symptoms of UTI may be atypical in this population*
Patients with indwelling urethral catheter	**No screening or treatment**, strong, low quality	Short term (<30d) catheter→ 3-5% bacteriuria per day Long term catheter→ up to 100% (!)

Nicolle LE , et al. Clin Infect Dis 2019; 68:e83–e110.

Who should get treated screened and treated for ASB?

- Pregnant women→ 2-7% will have ASB
  - Several studies in 1960-70's and metanalysis more recently showed treatment of ASB can reduce risk of pyelonephritis
  - Few old studies suggest possible reduced pre-term labor
  - IDSA suggests urine culture early in pregnancy
    - Rescreening later in those with negative culture or after short-course treatment is not recommended (lack of data)
- Patients undergoing urological surgery with high risk of breaching mucosal surfaces
  - This includes TURP/TURBT, ureteroscopy; NOT diagnostic cystoscopy or ureteral stent removal
  - These patients effectively have a contaminated surgical field and are at increased risk for symptomatic post-op UTI, upper tract infection and bacteremia

Nicolle LE , et al. Clin Infect Dis 2019; 68:e83–e110.

New Guidelines

Lyme Disease

Clinical Question #3

- A 37-year-old man with no PMH presents with malaise, low grade fever and a rash
- He noticed the rash 4 days after he received his first BNT162b2 (Pfizer–BioNTech) covid vaccine
- He lives in Maryland with his family and golden retriever who he walks in a local state park often

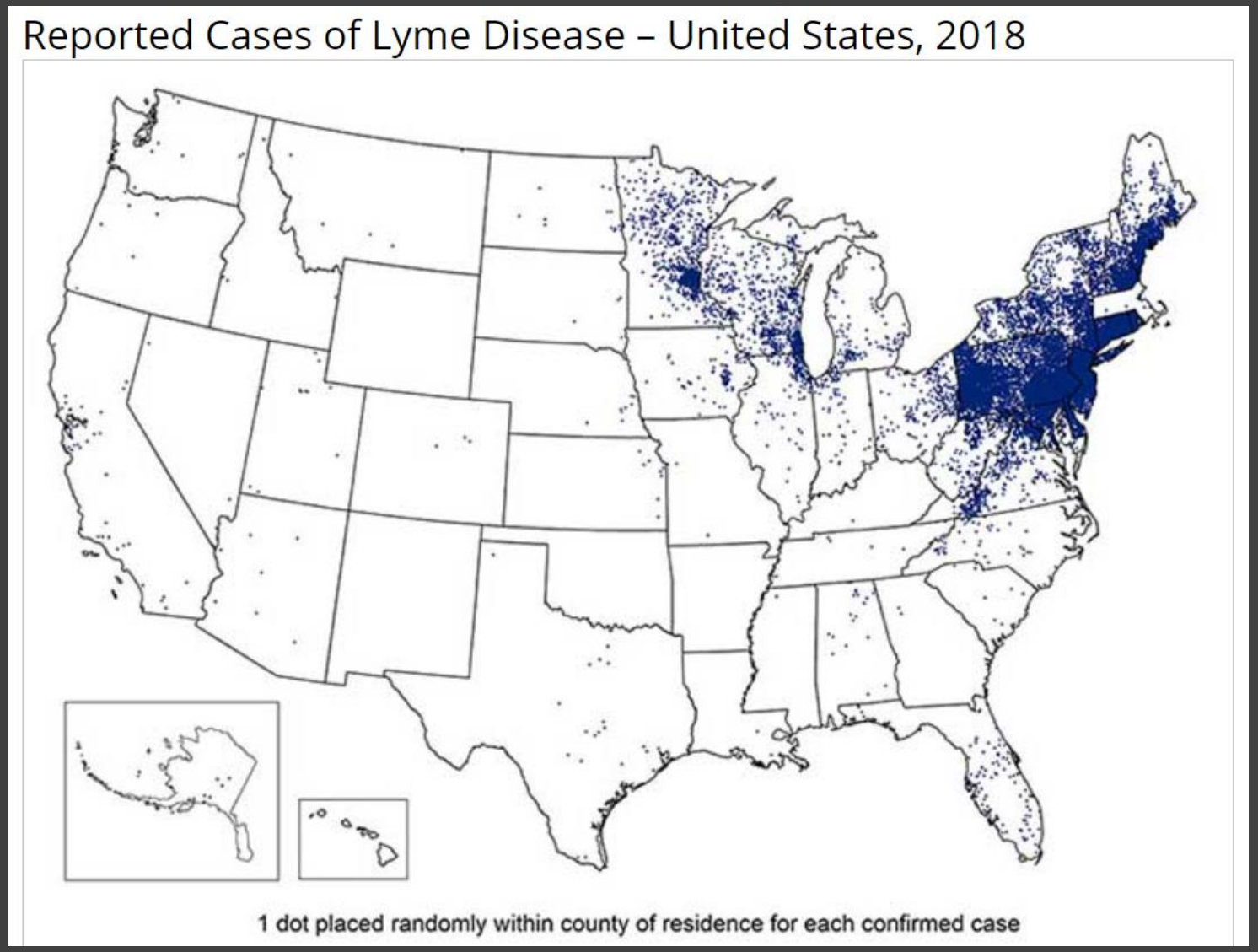
Dennison R, Novak C, Rebman A, et al. Cureus 11(12): e6509. doi:10.7759/cureus.6509

The best management of this rash is:

A. Test for Lyme disease with antibodies
B. Reassure him that his symptoms are related to his vaccine and will self-resolve
C. Test for Lyme disease with PCR testing
D. Treat with doxycycline for 10 days
E. Treat with cefuroxime for 14 days

Lyme Basics

- Lyme disease in US is due to infection with *Borrelia burdorferi* (and occasionally *B. mayonii*)
- Transmitted by Ixodes scapularis and to a lesser degree I. pacificus ticks
  - Typically transmitted by tick nymphs
  - Tick must be attached at least 36 hours to transmit
- I. scapularis can transmit several other infections
  - Anaplasma phagocytophilium, Babesia, B. miyamoti, and powassan



Lantos PM, et al. Clin Infect Dis. 2021 Jan 23;72(1):1-8.

https://www.cdc.gov/lyme/datasurveillance/maps-recent.html; accessed 4/16/22

Lyme Testing

- Recommended Testing: 2-tiered antibody testing which improves specificity
  - *Either:* Enzyme immunoassay (EIA) or indirect fluorescent antibody test (IFA) followed by IgM and IgG immunoblot testing
  - *Or:* Two different EIA tests sequential or concurrent
- When might testing not be reliable?
  - Early (<2 weeks) after infection antibodies may not be positive (positive as low as 20% of the time), particularly in patients with erythema migrans
  - Rarely, in humoral immunodeficiency, antibody may not be positive
    - Several reports of Lyme disease with negative serologies in those treated with rituximab
  - In patients with a history of Lyme disease, IgG can remain positive for years

Lantos PM, et al. Clin Infect Dis. 2021 Jan 23;72(1):1-8.
Wagemakers A, et al. BMC Inf Dis. 2018;18:362.
Sjowall J, et al. Front Neurol. 2021;12:645298

Lyme Testing Questions

- What about Lyme PCR?
  - No Lyme PCR test (for serum or CSF) has been cleared by FDA
  - If used, it should be adjunctive to standard testing and the test characteristics should be known
- What about CSF testing?
  - Serum antibody testing is still recommended first line for patients with CNS manifestations
  - If CSF obtained, serum:CSF antibody index is recommended
- What about EKG for patients who may have Lyme disease?
  - Carditis is typically symptomatic, so testing is only recommended for symptomatic patients

Lantos PM, et al. Clin Infect Dis. 2021 Jan 23;72(1):1-8.

Lyme Therapy

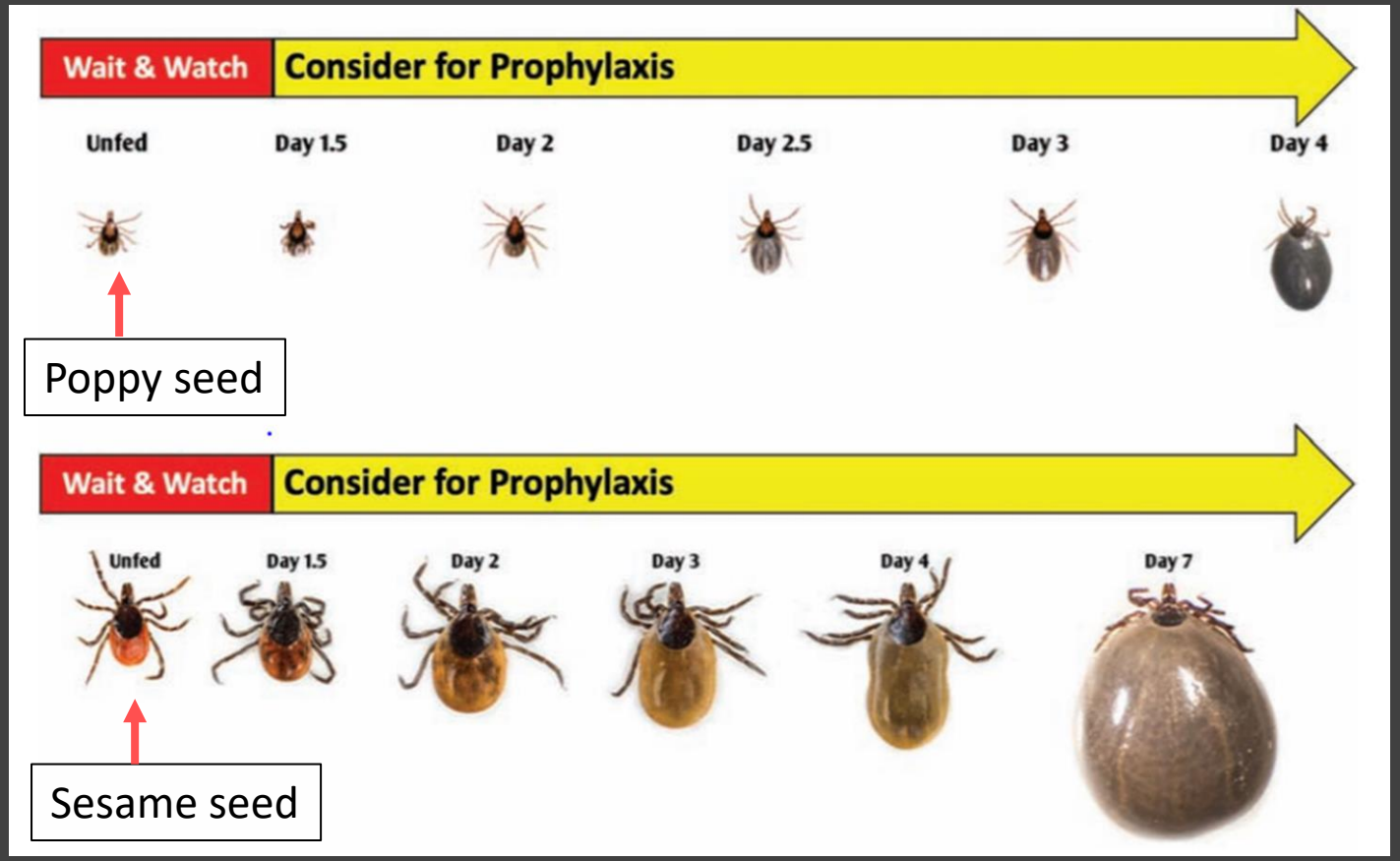
Table 4. Treatment of Specific Manifestations of Lyme Disease

Disease Manifestation	Route	Medication	Duration, days (range)[a]
Erythema migrans[b]	Oral	Doxycycline	10
		Amoxicillin or cefuroxime axetil	14
		Azithromycin[c]	7 (range: 5–10)
Meningitis or radiculopathy	Oral	Doxycycline	14–21
	IV[d]	Ceftriaxone	14–21
Cranial nerve palsy	Oral	Doxycycline	14–21
Carditis	Oral[e]	Doxycycline, amoxicillin, or cefuroxime axetil	14–21
	IV[e]	Ceftriaxone	14–21
Arthritis			
Initial treatment	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Recurrent or refractory arthritis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
	IV	Ceftriaxone	14[f]
Acrodermatitis chronica atrophicans	Oral	Doxycycline, amoxicillin, Or cefuroxime axetil	21–28
Borrelial lymphocytoma	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14

Lantos PM, et al. Clin Infect Dis. 2021 Jan 23;72(1):1-8.

Should I treat a patient with a documented tick bite and with what?

- Treatment criteria
  1. Tick must be *Ixodes spp*.
     - Nymphs and female adults most likely to transmit
  2. Bite occurred in endemic area
     - 20% of nymphs are infected with B. burdorferi in Northeast US
  3. Tick attached for >36 hours
- Treatment
  - Doxycyline 200 mg po x1 within 72 hours of the tick bite



Lantos PM, et al. Clin Infect Dis. 2021 Jan 23;72(1):1-8.

Summary

- **Oral antibiotics for serious infections**
  - There is growing evidence that oral antibiotics with good bioavailability can be used as step-down therapy to treat Gram-negative bacteremia
    - Oral beta-lactams have lower bioavailability
- **Short courses of antibiotics for Gram-negative bacteremia**
  - A growing body of data shows that 7 days of antibiotics can be used to treat uncomplicated controlled GNB in immunocompetent hosts
- **Asymptomatic bacteriuria**
  - Screening for bacteriuria in asymptomatic individuals is not indicated for a broad range of patients except pregnancy and patients undergoing invasive urological procedures
- **Lyme disease**
  - Erythema migrans is a clinical diagnosis; all other manifestations of Lyme disease first line diagnostics include standard 2-tier antibody testing
  - New treatment guidelines suggest shorter courses of therapy are adequate for early Lyme disease

Disclosures

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- I have been a consultant for biointelect (past) and F2G (current)

Selected References

- Principles of oral antibiotic use for serious infection
  - Beique L, Zvonar R. Can J Hosp Pharm. 2015;68:318-26.
- Use of oral and short courses of antibiotics for gram-negative bacteremia
  - Heil EL, Open Forum Infect Dis. 2021;8: ofab434
- Asymptomatic bacteriuria
  - Nicolle LE , et al. Clin Infect Dis 2019; 68:e83–e110.
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