Guidance on management of uncomplicated bloodstream infections from Gram-negative organisms

Detection of Gram-negative organisms in the blood is common in hospitalized patients and should not be considered a contaminant as a general rule. Gram-negative bloodstream infection (GN-BSI) can be life threatening and should be treated promptly. These infections can be categorized as complicated or uncomplicated. **Uncomplicated GN-BSI** is defined as patients without evidence of endocarditis, endovascular disease, central nervous system or osteoarticular infection. Lack of clinical improvement or persistent bacteremia may indicate a complicated GN-BSI and adequate source control should be investigated further. A growing body of literature supports that uncomplicated GN-BSI can be effectively cured with shorter durations of antimicrobial therapy than previously utilized[1-3]. Additionally, patients can successfully be transitioned to oral antimicrobial therapy (OAT) for definitive management if a highly bioavailable oral option is available[4-9].

GN-BSI Candidates for Short Course & Oral Therapy:

Patients that meet all of the following criteria may be candidates for both treatment with 7 days of total antimicrobial therapy and early switch from IV to oral antibiotics:

- ❑ GN-BSI from an organism other than *Salmonella* spp., *Acinetobacter* spp., or *Stenotrophomonas* spp. (Patients with infections from these bacteria may be candidates for transition to oral antibiotics, however longer durations may be needed)
    - **Recommend ID consultation** for noted exceptions.
- ❑ No evidence of endovascular infection, unresected osteomyelitis, central nervous system infection or retained prosthetic material (e.g. urinary stents) at site of infection. Patients with these complicated infections may be candidates for transition to oral antibiotics, but longer durations are recommended.
    - **Recommend ID consultation** for noted exceptions.
- ❑ Causative organism is known to be susceptible to at least one recommended oral agent
    - Patients who do not have an oral option are still candidates for 7-day treatment with an active IV agent
- ❑ Patient is able to tolerate oral (PO) medications without concern for poor gastrointestinal absorption
- ❑ Patient is clinically improving on current antibiotics; hemodynamically stable without vasopressor use
- ❑ Adequate source control has been achieved, if needed. Examples include:
    - **UTI:** exchange or removal of urinary catheter/nephrostomy tubes present when infection developed, resolution of any known obstruction
    - **Intra-abdominal infection:** drainage of abscesses/infected fluid collections, debridement of infected tissues
    - **Skin and soft tissue infection:** Drainage of abscesses or fluid collections, debridement or amputation of necrotic tissues

- **Line associated bacteremia:** Removal or exchange of catheter if failure to improve or if persistently positive blood cultures (see below for repeat blood culture guidance).
  - **If line is retained, patient can be a candidate for oral antibiotic therapy, however a longer duration may be required.**
- If uncertain about source control, **consult Infectious Diseases service**

Repeat blood cultures

For GN-BSI, follow up blood cultures are unnecessary in most patients who are improving clinically on antibiotic therapy[10]. Select patients who may be candidates for follow up blood cultures include those with persistent fevers (when identified organism(s) susceptible to given antimicrobial), concern for endovascular infection, retained intravascular catheters or other prosthetic devices, and those who have not otherwise clinically improved. Repeat blood cultures should not be obtained until at least 48 hours after initial blood cultures.

Oral therapy antibiotic choice and doses recommended for IV-PO switch

Treatment selection should be guided by antibiotic susceptibility data. It is important that bioavailable oral agents are used at doses that will achieve adequate concentrations to treat systemic infection.

Preferred oral therapies for uncomplicated GN-BSI:

- Levofloxacin 750mg PO daily
- Trimethoprim/sulfamethoxazole (TMP/SMX) 7-10 mg/kg TMP based on Adjusted Body Weight (AdjBW) rounded to nearest double strength (DS, 160mg) tablet size:
  - 40-49kg AdjBW: 1 DS tablet BID PO
  - 50-69kg AdjBW: 1 DS tablet TID PO
  - 70-95kg AdjBW: 2 DS tablet BID PO
  - >95kg AdjBW: call antimicrobial stewardship pharmacist
- AdjBW is equal to ideal body weight (IBW) plus 40% of the difference between total and IBW

Alternative therapies, in order of preference (utilize if patient has a medication contraindication or non-susceptible organism to preferred agents, and organism is susceptible)

- Amoxicillin 1g TID PO*
- Cephalexin 1g TID PO or Cefadroxil 1g BID PO**
- Amoxicillin/clavulanate 875/125mg TID PO

*Ampicillin susceptibility can be utilized to determine susceptibility to oral amoxicillin.

Cefazolin susceptibility can be utilized to determine susceptibility to oral cephalosporins (cephalexin and cefadroxil). **Ceftriaxone should not be utilized as a surrogate for susceptibility of oral cephalosporins.

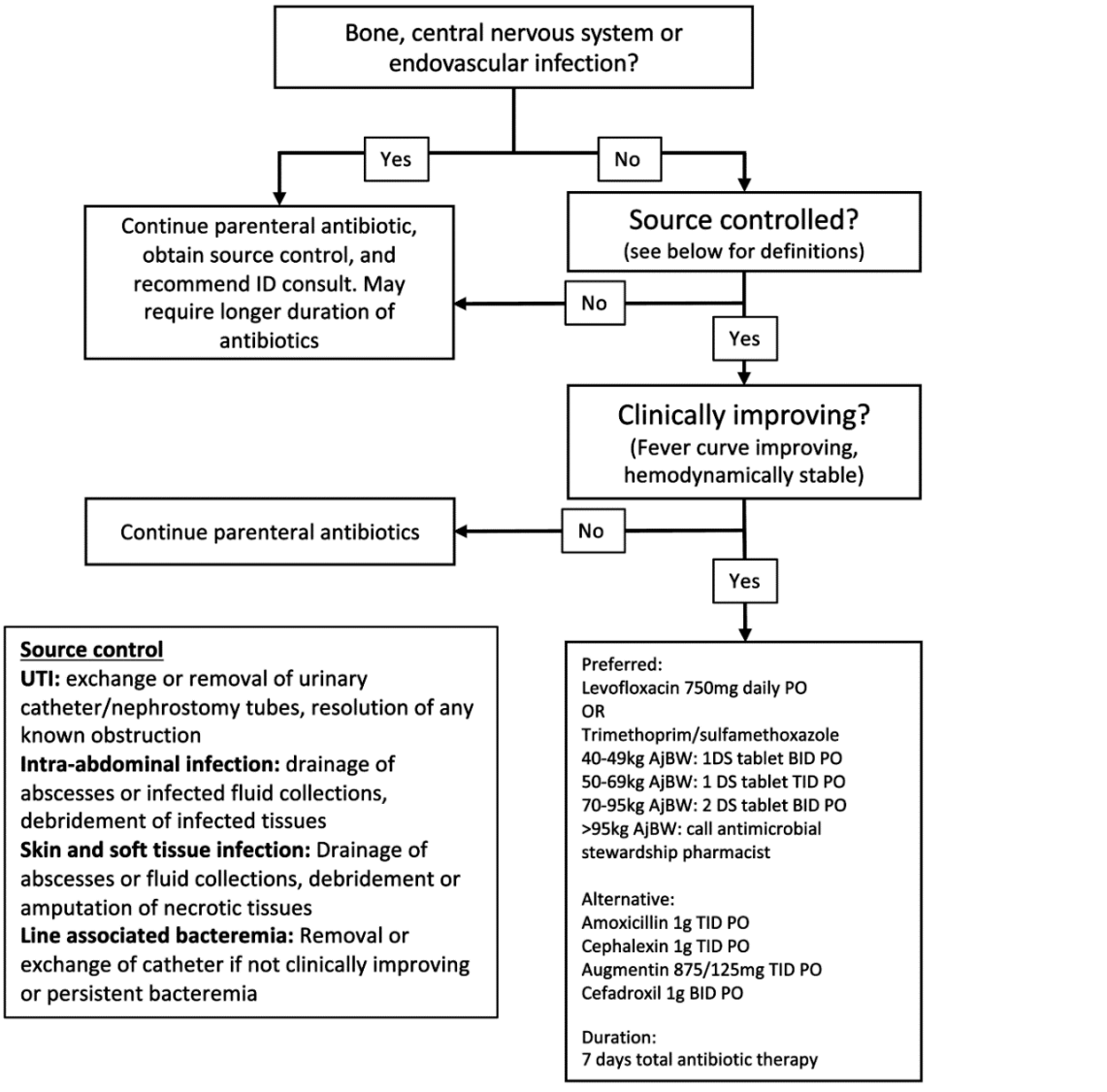
Agents generally not recommended as oral therapy for GN-BSI:

Penicillin VK	Ampicillin
Cefuroxime	Doxycycline
Cefdinir	Fosfomycin
Cefpodoxime	Nitrofurantoin

Duration of therapy

Several studies have demonstrated that treatment durations of 7 days result in outcomes equivalent to 14 days in uncomplicated GN-BSI (both oral and intravenous antibiotics). Immunocompromised patients have often been excluded from these studies; however, when included no difference in any clinical outcomes with shorter antibiotic durations were noted [11]. Thus, we do not recommend extending duration of therapy in uncomplicated GN-BSI due to immunocompromised status alone. If clinical uncertainty exists or if the bloodstream infection is due to an endovascular infection, CNS infection, osteomyelitis without complete resection, or lacks source control, ID consult is recommended, as these exceptions may require longer duration of therapy. Bacteremia secondary to pyelonephritis may require a longer duration of 10-14 days if utilizing trimethoprim-sulfamethoxazole or a beta-lactam agent for definitive therapy[12].

Figure 1: Treatment decision algorithm



Note: Antibiotic selection should be guided by antibiotic susceptibility

Summary of the literature:

Highly bioavailable oral agents have been shown to be equivalent to intravenous (IV) options in the definitive management of GN-BSI. Several studies have shown no difference in clinical failure, microbiological failure, or recurrent infection in patients transitioned to oral antibiotics[4-9]. These studies also demonstrate shorter length of stay when transitioned to oral antimicrobial therapy[4-8]. Intravenous catheters have been associated with significant complications which may be avoided by transitioning to oral antibiotics[6,13]. Transitioning to oral antibiotics has also been associated with decreased healthcare costs[8].

Many studies evaluated transition to oral antibiotics at 72 hours without increase of treatment failure, allowing for susceptibility data to return[4,5,7]. One study demonstrated that there was no difference in outcomes with longer IV antibiotic lead-in than those with short IV lead-in, suggesting that patients are candidates for transition to oral when clinically stable and antimicrobial susceptibilities have returned[14].

Some organisms have been frequently excluded from these trials either due to their susceptibility profiles (*Acinetobacter* spp. and *Stenotrophomonas* spp.) or risk for metastatic site of infection (*Salmonella* species)[2,3]. Although these organisms frequently have a viable oral option, antibiotic recommendations may be more complex and utilize a different duration than other gram-negative organisms. Recent IDSA guidance recommend combination therapy for severe infections with *Stenotrophomonas* species[15]. These decisions can be complex, and infectious disease input is recommended. Multidrug resistant *Acinetobacter baumanii* has been of increasing concern, particularly amongst patients that receive high volume care[16]. To date, Nebraska Medicine's antibiogram demonstrates retained susceptibility to most active antibiotics, although overall sample size is low, therefore we recommend ID consultation to help determine which patients may be candidates for transition to oral antibiotics. Invasive salmonellosis should prompt investigation for metastatic foci of infection, as lone gastrointestinal disease rarely results in bacteremia, so we recommend infectious disease consultation to assist in this work up as well[17].

<u>Selection of Agent:</u>

Agents such as fluoroquinolones and TMP/SMX have high oral bioavailability, with the oral agent clinically equivalent to IV (table 1). While most oral antibiotic studies focused on these agents, accumulating evidence suggests that high-dose oral beta-lactams are equivalent in clinical success and mortality[14,18-20]. There are some data suggesting that beta-lactams are associated with higher rates of BSI recurrence[14,20], but this effect may be mitigated when a higher dose is used. Pharmacokinetic data supports the use of amoxicillin, cephalexin, and amoxicillin/clavulanate if optimal dosing is utilized[10] (table 1). In addition, studies utilizing these agents have <u>not</u> had increased clinical failure or mortality[9,14,18-20]. Oral beta lactams typically have safer adverse effect profiles when compared to fluoroquinolones or TMP/SMX[18]. Thus, fluoroquinolone and TMP/SMX are preferred, but oral beta-lactams are reasonable alternatives in patients at increased risk for fluoroquinolone or TMP/SMX adverse effects, have drug interactions, or where resistance precludes their use.

Some oral antibiotics do not have pharmacokinetic data that supports their use for GNB. Although doxycycline is highly bioavailable, it does not reach effective concentrations in the serum, making it a poor choice for GNB[10]. Some beta-lactams have low oral bioavailability or do not have sufficient data to recommend their usage (table 1). These inadequate options include cefpodoxime, cefuroxime, and cefdinir[10].

Table 1. Bioavailability of antibiotics and recommended doses for early oral therapy to treat patients with GN-BSI[10,21]

Non-Beta Lactam Agents with High Oral Bioavailability	Absorption	Recommended Doses
Levofloxacin	99%	750mg PO daily
Ciprofloxacin (Non-formulary)	70%	500mg BID (750mg po BID for Pseudomonas)
Trimethoprim (TMP)/ Sulfamethoxazole	85%	7-10 mg/kg/d of TMP in divided doses 40-49kg AdjBW: 1DS tablet PO BID 50-69kg AdjBW: 1 DS tablet PO TID 70-95kg AdjBW: 2 DS tablet PO BID >95kg AdjBW: Call antimicrobial stewardship pharmacist Pager: 888-0349
Metronidazole – for anaerobes only	>90%	500mg PO TID
Beta-lactams with High Oral Bioavailability		
Amoxicillin	74-92%	1g PO TID
Amoxicillin-Clavulanate	60%	875/125mg PO TID
Cephalexin	90-100%	1g PO TID
Cefadroxil	90%	1g PO BID
Beta-lactams with Low Oral Bioavailability		
Cefdinir	21-25%	Not recommended
Cefpodoxime (Non-formulary)	29-53%	Not recommended
Cefuroxime	30-52%	Not recommended

Duration of Therapy:

Several studies have demonstrated that 7 days of therapy achieves equivalent outcomes to 14 days[1-3]. Studies demonstrate no difference in mortality, complications, side effects, or length of stay between those that were treated with 7 vs. 14 days[1,2]. One study also reported shorter time to return to baseline with a shorter antibiotic course[2]. One retrospective study revealed increased odds of recurrence in patients with bacteremia associated with complicated UTI in patients treated with shorter courses of antibiotics (7 vs. 14 days), however, this difference resolved when only patients on highly bioavailable oral agents were included[22]. Bacteremia associated with pyelonephritis may require a longer duration of 10-14 days if utilizing trimethoprim-sulfamethoxazole or oral beta-lactam antibiotics[12].

Most studies exclude patients with immunocompromising conditions, but some data are available. Immunocompromised patients have been represented in small numbers in RCTs, with no difference in mortality, bloodstream infection relapse, or rehospitalization noted in systematic review compared to immunocompetent patients[1,2,23]. One prospective observational study evaluated long versus short courses of antibiotics for GN-BSI in immunocompromised hosts found no difference in mortality or recurrence of bacteremia and decreased length of stay in the short course cohort, similar to immunocompetent hosts[11]. One retrospective study evaluating shorter antibiotic therapy in GN-BSI in patients with neutropenia revealed no difference in a composite outcome of all-cause mortality and microbiologic relapse within 90-days[24].

When clinical uncertainty exists regarding adequate source control of a GN-BSI in immunocompromised persons, infectious diseases consultation is recommended.

Repeat Blood Cultures:

Experts agree and the available data support that repeat blood cultures are unnecessary in patients with GNB if they are clinically improving on therapy[10]. In one study, persistent bacteremia was associated with endovascular infection and inability to obtain source control at 48 hours. Follow up blood cultures were low yield in patients with GN-BSI[25]. In addition, several retrospective evaluations of follow-up blood cultures have demonstrated prolonged length of stay and antibiotic duration[26,27]. Situations where repeat cultures may be appropriate include patients without an appropriate clinical response in 72 hours on appropriate antibiotic therapy, in patients with concern for endocarditis or endovascular infections, or patients in which adequate source control is not able to be obtained (retained material)[10]. For further institutional guidance on follow-up blood culture recommendations: https://www.unmc.edu/intmed/_documents/id/asp/unmc_follow-up_bcx_algorithm_-_final.pdf

Developed by Mackenzie Keintz, MD: July 2023

Reviewed by Scott Bergman, PharmD; Jasmine Marcelin, MD; Molly Miller, PharmD; Jonathon Ryder, MD; Erica Stohs, MD; Trevor Van Schooneveld, MD; Bryan Alexander, PharmD, Jeremy Tigh, PharmD

Approved by Antimicrobial Stewardship Committee: August 2023

References

1. Molina J, Montero-Mateos E, Praena-Segovia J, et al. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. *Clin Microbiol Infect*. Apr 2022;28(4):550-557. doi:10.1016/j.cmi.2021.09.001

2. Yahav D, Franceschini E, Koppel F, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. *Clin Infect Dis*. Sep 13 2019;69(7):1091-1098. doi:10.1093/cid/ciy1054
3. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. *JAMA*. Jun 02 2020;323(21):2160-2169. doi:10.1001/jama.2020.6348
4. Park TY, Choi JS, Song TJ, Do JH, Choi SH, Oh HC. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. *Dig Dis Sci*. Nov 2014;59(11):2790-6. doi:10.1007/s10620-014-3233-0
5. Rieger KL, Bosso JA, MacVane SH, Temple Z, Wahlquist A, Bohm N. Intravenous-only or Intravenous Transitioned to Oral Antimicrobials for Enterobacteriaceae-Associated Bacteremic Urinary Tract Infection. *Pharmacotherapy*. Nov 2017;37(11):1479-1483. doi:10.1002/phar.2024
6. Thurber KM, Arnold JR, Narayanan PP, Dierkhising RA, Sampathkumar P. Comparison of intravenous and oral definitive antibiotic regimens in hospitalised patients with Gram-negative bacteraemia from a urinary tract infection. *J Glob Antimicrob Resist*. Sep 2019;18:243-248. doi:10.1016/j.jgar.2019.03.013
7. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. *JAMA Intern Med*. Mar 01 2019;179(3):316-323. doi:10.1001/jamainternmed.2018.6226
8. Amodio-Groton M, Madu A, Madu CN, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. *Ann Pharmacother*. Jun 1996;30(6):596-602. doi:10.1177/106002809603000605
9. Al-Hasan MN, Rac H. Transition from intravenous to oral antimicrobial therapy in patients with uncomplicated and complicated bloodstream infections. *Clin Microbiol Infect*. Mar 2020;26(3):299-306. doi:10.1016/j.cmi.2019.05.012
10. Heil EL, Bork JT, Abbo LM, et al. Optimizing the Management of Uncomplicated Gram-Negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process. *Open Forum Infect Dis*. Oct 2021;8(10):ofab434. doi:10.1093/ofid/ofab434
11. Herrera F, Torres D, Carena A, et al. Short Course of Antibiotic Therapy for Gram-Negative Bacilli Bacteremia in Patients with Cancer and Hematopoietic Stem Cell Transplantation: Less Is Possible. *Microorganisms*. Feb 17 2023;11(2)doi:10.3390/microorganisms11020511
12. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. Mar 1 2011;52(5):e103-20. doi:10.1093/cid/ciq257
13. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. *Am J Med*. Aug 2012;125(8):733-41. doi:10.1016/j.amjmed.2012.04.010
14. Kutob LF, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. *Int J Antimicrob Agents*. Nov 2016;48(5):498-503. doi:10.1016/j.ijantimicag.2016.07.013
15. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. *Clin Infect Dis*. Jul 06 2022;74(12):2089-2114. doi:10.1093/cid/ciab1013
16. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Accessed November 4, 2022. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

17. Fierer J. Invasive Non-typhoidal Salmonella (iNTS) Infections. *Clin Infect Dis*. Sep 10 2022;75(4):732-738. doi:10.1093/cid/ciac035
18. Mercuro NJ, Stogsdill P, Wungwattana M. Retrospective analysis comparing oral stepdown therapy for enterobacteriaceae bloodstream infections: fluoroquinolones versus β-lactams. *Int J Antimicrob Agents*. May 2018;51(5):687-692. doi:10.1016/j.ijantimicag.2017.12.007
19. Nisly SA, McClain DL, Fillius AG, Davis KA. Oral antibiotics for the treatment of Gram-negative bloodstream infections: A retrospective comparison of three antibiotic classes. *J Glob Antimicrob Resist*. Mar 2020;20:74-77. doi:10.1016/j.jgar.2019.07.026
20. Mponponsuo K, Brown KA, Fridman DJ, et al. Highly versus less bioavailable oral antibiotics in the treatment of gram-negative bloodstream infections: a propensity-matched cohort analysis. *Clin Microbiol Infect*. Apr 2023;29(4):490-497. doi:10.1016/j.cmi.2022.10.004
21. Mogle BT, Beccari MV, Steele JM, Fazili T, Kufel WD. Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections. *Expert Opin Pharmacother*. Jun 2019;20(8):903-907. doi:10.1080/14656566.2019.1594774
22. McAteer J, Lee JH, Cosgrove SE, et al. Defining the Optimal Duration of Therapy for Hospitalized Patients With Complicated Urinary Tract Infections and Associated Bacteremia. *Clin Infect Dis*. May 03 2023;76(9):1604-1612. doi:10.1093/cid/ciad009
23. Turjeman A, von Dach E, Molina J, et al. Duration of antibiotic treatment for Gram-negative bacteremia - Systematic review and individual participant data (IPD) meta-analysis. *EClinicalMedicine*. Jan 2023;55:101750. doi:10.1016/j.eclinm.2022.101750
24. Ranganath N, Yetmar ZA, McCandless AR, et al. Evaluating antimicrobial duration for Gram-negative bacteremia in patients with neutropenia due to hematologic malignancy or hematopoietic stem cell transplantation. *Transpl Infect Dis*. Jun 06 2023:e14085. doi:10.1111/tid.14085
25. Wiggers JB, Xiong W, Daneman N. Sending repeat cultures: is there a role in the management of bacteremic episodes? (SCRIBE study). *BMC Infect Dis*. Jun 13 2016;16:286. doi:10.1186/s12879-016-1622-z
26. Mitaka H, Fujitani S, Kuno T, Perlman DC. Association between follow-up blood cultures for gram-negative bacilli bacteremia and length of hospital stay and duration of antibiotic treatment: A propensity score-matched cohort study. *Infect Control Hosp Epidemiol*. Mar 2023;44(3):474-479. doi:10.1017/ice.2022.110
27. Canzoneri CN, Akhavan BJ, Tosur Z, Andrade PEA, Aisenberg GM. Follow-up Blood Cultures in Gram-Negative Bacteremia: Are They Needed? *Clin Infect Dis*. Nov 13 2017;65(11):1776-1779. doi:10.1093/cid/cix648