Best Practices in the Diagnosis and Treatment of Bacteremia
Acute Care

Slide Title and Commentary	Slide Number and Slide
Best Practices in the Diagnosis and Treatment of Bacteremia **Acute Care** SAY: This presentation will address best practices in the diagnosis and management of bacteremia.	**Slide 1**
Objectives SAY: By the end of this presentation, participants will be able to: • Review recommendations for appropriate blood culture collection • Develop organism-specific management recommendations for bacteremia • Discuss opportunities for de-escalation of antibiotic therapy for bacteremia • Discuss reasonable durations of antibiotic therapy for common organisms causing bacteremia	**Slide 2**

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The Four Moments of Antibiotic Decision Making SAY: In the presentation titled "Best Practices in the Diagnosis and Management of Sepsis," moments 1 and 2 of the Four Moments of Antibiotic Decision Making are reviewed. That presentation reviews when clinicians should have a high pretest probability of bacteremia, when to order blood cultures, and empiric antibiotic therapy considerations. The current presentation focuses on moments 3 and 4 — antibiotic decision making in response to positive blood cultures.	**Slide 3**

Obtaining Appropriate Blood Cultures	**Slide 4**
SAY: Before we focus on specific organisms, it is important to review indications for blood culture collection. Blood cultures should not be obtained indiscriminately because this increases the number of contaminated blood cultures, leading to unnecessary antibiotic therapy. Rather, specific criteria should be met to warrant obtaining blood cultures. Blood cultures should be obtained for patients presenting with severe sepsis or septic shock, specifically those meeting systemic inflammatory response syndrome, or SIRS, criteria plus suspected infection with organ dysfunction or a lactate greater than 2 mmol/L, or meeting other more recent definitions for severe sepsis. Additionally, blood cultures are recommended for infectious processes commonly associated with bacteremia, including: cholangitis, meningitis, pyelonephritis, severe pneumonia, suspected endocarditis or endovascular infections, vertebral osteomyelitis or discitis, severe skin and soft-tissue infections, vertebral osteomyelitis or discitis, systemic infection in the setting of asplenia, or suspected catheter-related bloodstream infections. Finally, blood cultures should be obtained for patients with a new fever with a temperature greater than or equal to 38.5 degrees Celsius or 101.2 degrees Fahrenheit and at least one other sign or symptom of infection, in the absence of a known alternative diagnosis, for patients who have not had blood cultures obtained in the previous 48 hours. Two sets of peripheral blood cultures should be obtained, with each set consisting of an aerobic	

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and anaerobic bottle. Cultures from central lines are always discouraged, as these are more likely to yield contaminants. The diagnostic yield increases with increasing numbers of blood cultures. In one study including 351 episodes of bacteremia with at least 4 blood cultures obtained during a 24-hour period, 73 percent of bacteremic episodes were detected with one blood culture, 94 percent were detected with two blood cultures, 97 percent were detected with three blood cultures, and greater than 99 percent were detected with four blood cultures. For patients with a new infectious process not meeting the above criteria (for example, a low-risk patient admitted to the general wards with community-acquired pneumonia) blood cultures are generally not recommended as the yield is low. For patients with persistent fevers with two sets of negative blood cultures within the past 48 hours, blood cultures are generally not warranted. Similarly, for patients with isolated vital sign changes, it is important to monitor patients first and consider other contributing factors, such as dehydration leading to tachycardia, before deciding to obtain blood cultures.	

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Interpretation of Positive Blood Cultures SAY: Certain organisms should never be considered contaminants when recovered from blood cultures. Namely, *Staphylococcus aureus*, Gram-negative rods, and Candida species. On the opposite end of the spectrum, organisms such as coagulase-negative Staphylococcus and Gram-positive rods like Corynebacterium or Diphtheroids usually do not require treatment because they are common skin contaminants. However, they may represent endovascular infections in patients with indwelling hardware (e.g., catheters, prosthetic valves) who have signs and symptoms of infection. In these cases, bacteria are usually growing in more than one blood culture set. Additional blood cultures should be obtained before starting antibiotics if there is clinical uncertainty. Some organisms may represent either true infection or contamination. These include viridans group streptococci and *Enterococcus* species. These organisms can be found as normal inhabitants of the gut, and in hospitalized patients they can contaminate the skin and subsequently grow in blood cultures. On the other hand, they can also cause true infection. It is important to evaluate the clinical picture of the patient when making treatment decisions. Look for a possible source—gastrointestinal pathology, oral pathology, endocarditis—along with signs and symptoms of infection. Patients with endovascular infections will generally have persistently positive blood cultures.	**Slide 5**

Slide Title and Commentary	Slide Number and Slide
E*nterobacteriaceae* Bacteremia: Diagnosis SAY: Let's shift focus to discuss common organisms causing bacteremia, beginning with the *Enterobacteriaeceae*. The most common *Enterobacteriaceae* are *E. coli*, *Klebsiella* species, *Enterobacter* species, *Serratia* species, and *Citrobacter* species. Most will be identified as lactose-fermenting Gram-negative organisms by the microbiology lab before they are speciated. Identifying the source of bacteremia is critical so that appropriate approaches to source control can be undertaken. The most common sources of *Enterobacteriaceae* in hospitalized patients are urine, intra-abdominal, and pulmonary. *Enterobacteriaceae* bacteremia can also occur via translocation from the gut due to gut disruption or procedures like the placement of biliary stents.	**Slide 6**

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Enterobacteriaceae Bacteremia: Antibiotic Therapy
 	
SAY:
 	
When treating *Enterobacteriaceae* bacteremia, narrow therapy based on antibiotic susceptibility results. For example, if the organism is susceptible to a narrow agent such as ampicillin or cefazolin and intravenous or IV therapy is still needed, switch to these agents preferentially over broader spectrum agents.
 	
Additionally, consideration should be given as to whether patients may be eligible to transition to oral therapy. A multicenter observational study including 739 patients with *Enterobacteriaceae* bacteremia from a variety of sources who remained on IV therapy for their entire treatment duration versus 739 patients who were transitioned to oral step-down therapy showed similar clinical outcomes of mortality and recurrent bacteremia within 30 days for both groups. To be eligible for oral step-down therapy, patients had to have an appropriate clinical response to therapy by day 5 and had to have appropriate source control, which was defined as removal of infected hardware, drainage of infected fluid collections, or resolution of obstruction for biliary or urinary sources.
 	
When considering oral step-down therapy, antibiotics with high bioavailability like fluoroquinolones or trimethoprim/sulfamethoxazole are recommended, if the organism is susceptible *in vitro*.
	Slide 7
	
	Enterobacteriaceae Bacteremia: Antibiotic Therapy
	
	• Narrow therapy based on susceptibility results
	• Considerations for IV to PO conversion:[3]
	   – Patient has an appropriate clinical response
	   – Appropriate source control preferred
	   – Patient needs to be able to take and absorb oral antibiotics
	   – Active oral antibiotic needs to have adequate oral bioavailability
	      o Fluoroquinolones, trimethoprim/sulfamethoxazole
	
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Enterobacteriaceae Bacteremia: Treatment Duration
 	
Ten to 14 days has traditionally been used for the treatment of Gram-negative bacteremia. However, a randomized controlled trial including 604 patients with Gram-negative bacteremia randomized to receive either 7 days or 14 days of treatment—most of which were *Enterobacteriaceae*—found that for patients who were afebrile and hemodynamically stable and had achieved appropriate source control, 1 week of antibiotic therapy was sufficient. Similar results were seen in a multicenter cohort study; this study is discussed in the "Best Practices in the Diagnosis and Treatment of Diverticulitis and Biliary Tract Infections" presentation.
	Slide 8
	
	Enterobacteriaceae Bacteremia: Duration of Therapy
	
	• Traditional treatment duration has been 10–14 days
	• Randomized controlled trial including 604 patients with Gram-negative bacteremia randomized to receive either 7 days or 14 days of treatment[4,5]
	  – Most of the organisms were *Enterobacteriaceae*
	  – For patients who were afebrile, hemodynamically stable, and achieved appropriate source control, 1 week of antibiotic therapy was sufficient.
	
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Enterobacteriaceae Bacteremia: Management
 	
SAY:
 	
There is a minimal role for followup blood cultures in patients with Gram-negative bacteremia. In a study of 500 episodes of bacteremia that did not include contaminants, 77 percent had at least one followup blood culture. Of these, only eight grew Gram-negative rods. In contrast to patients with *Staph aureus* bacteremia, followup blood cultures should not be obtained routinely for *Enterobacteriaceae* bacteremia; consider followup cultures if there are persistent symptoms despite source control or if there is suspicion for an endovascular infection.
	Slide 9
	
	Enterobacteriaceae Bacteremia: Followup Cultures
	
	• Minimal role for followup blood cultures in Gram-negative bacteremia
	• Study evaluating 500 episodes of bacteremia[6]
	  – 77% had at least one followup blood culture
	  – Only eight cultures grew Gram-negative rods
	  – Do not need to obtain routinely
	  – Consider if persistent symptoms despite source control or suspicion of endovascular infection
	
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Extended-Spectrum Beta-Lactamases (ESBLs) SAY: It's important to be aware of some common resistance mechanisms seen in *Enterobacteriaceae*. Extended-spectrum beta-lactamase or ESBL production is most commonly seen in *E. coli*, *Klebsiella* species, and *Proteus* species. Some laboratories perform ESBL confirmatory testing, and it may be noted in the microbiology report if an organism is an ESBL producer. The agents of first choice for ESBL bacteremia are carbapenems. This is based on the results of a multicenter randomized controlled trial comparing the use of meropenem versus piperacillin/tazobactam for the treatment of ESBL bacteremia. These data are generally extrapolated to any invasive ESBL infection. Fluoroquinolones and trimethoprim/sulfamethoxazole could be considered for ESBL cystitis or as step-down therapy, if the organism is susceptible. Ceftriaxone, cefepime, and aztreonam are not recommended, even if susceptible, as they are associated with a higher risk of failure than carbapenems.	**Slide 10** ### Extended-Spectrum Beta-Lactamases • Most commonly seen in *E. coli*, *Klebsiella* species, *Proteus* species • Many microbiology laboratories are not performing ESBL confirmation testing • Agents of first choice for invasive infections are carbapenems, based on the results of a multicenter randomized trial[7] • Can consider fluoroquinolones or trimethoprim/sulfamethoxazole if susceptible • Can consider piperacillin/tazobactam, if susceptible, for milder infections like cystitis • Ceftriaxone, cefepime, and aztreonam not recommended AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 10

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AmpC Beta-Lactamases SAY: Another type of resistance mechanism we see with *Enterobacteriaceae* is production of AmpC beta-lactamases. These are most commonly seen in *Enterobacter* species (and less commonly with *Serratia marcescens* and *Citrobacter* species). They are induced by exposure to third-generation cephalosporins like ceftriaxone or ceftazidime. Third-generation cephalosporins are not recommended for the treatment of *Enterobacter* species even if reported as susceptible because resistance during therapy is anticipated to occur in about 20 to 30 percent of cases. Microbiology laboratories do not test for AmpC beta-lactamases. For invasive *Enterobacter* species infections, consider treating with cefepime or carbapenems. Fluoroquinolones or trimethoprim/sulfamethoxazole can also be considered, if the organism is susceptible.	**Slide 11** **AmpC Beta-Lactamases** • Most commonly seen in *Enterobacter* species • Induced by exposure to third-generation cephalosporins: do NOT use these agents to treat *Enterobacter* species even if reported as susceptible • Microbiology laboratories do not test for AmpC beta-lactamases • For invasive *Enterobacter* species infections, avoidance of third-generation cephalosporins is recommended – Consider cefepime,[8,9] carbapenems, fluoroquinolones, or trimethoprim/ sulfamethoxazole, if susceptible AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 11

Carbapenem-Resistant *Enterobacteriaceae*	Slide 12

Carbapenem-Resistant *Enterobacteriaceae*

SAY:

Carbapenem-resistant *Enterobacteriaceae* or CRE are *Enterobacteriaceae* resistant to at least one carbapenem, such as ertapenem, meropenem, imipenem/cilastatin, or doripenem. About half the time they are carbapenem-resistant because they produce carbapenemase enzymes. Carbapenemase enzymes hydrolyze the beta-lactam ring of beta-lactam antibiotics, causing them to become inactive. The most common carbapenemases encountered in the United States are KPCs or *Klebsiella pneumoniae* carbapenemases. These can be produced by any *Enterobacteriaceae* and are not just limited to *Klebsiella pneumoniae*. Microbiology laboratories may or may not test for carbapenemase production and may or may not be able to specifically identify KPCs. Regardless, if you are taking care of a patient growing a CRE, an infectious diseases consult is recommended.

There are some general rules to consider with treating CRE infections. Some antibiotic agents that became commercially available after 2015, such as the beta-lactam/beta-lactamase inhibitor combinations ceftazidime/avibactam, meropenem/vaborbactam, and imipenem-cilastatin/relebactam appear to have good activity as single agents against CRE. Empiric use of these agents should be considered if patients are known to be colonized with CRE, have clear epidemiologic risk factors for a CRE infection (e.g., part of a known outbreak or travel to an endemic area), or if there is strong clinical concern for severe CRE infection (e.g., new hemodynamic instability in the setting of prolonged carbapenem therapy). Routine empiric use should be discouraged to avoid the emergence of resistance to these agents, which has already been observed. Thus, susceptibility testing should always be obtained when using these agents.

For hospitals that do not readily have access to these agents, other regimens can be considered while CRE-active beta-lactam agents are being obtained. For example, another option for the treatment of CRE infections is the use of extended-infusion meropenem or imipenem/cilastatin if the organism's meropenem or imipenem minimum inhibitory concentration, or MIC, is

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Carbapenem-Resistant *Enterobacteriaceae*

- CRE are resistant to at least one carbapenem
  - e.g., ertapenem, meropenem, imipenem/cilastatin, or doripenem
- About half the time they produce carbapenemase enzymes[10]
  - KPC carbapenemases are the most common carbapenemases in the United States
- Consult infectious diseases for treatment recommendations
- Some general rules:[11-14]
  - Beta-lactam/Beta-lactamase inhibitor combination agents (e.g., ceftazidime/avibactam, meropenem/vaborbactam), generally have good activity against CRE and are the preferred treatment
    - Must obtain susceptibility testing
  - Other options if CRE-active beta-lactam/beta-lactamase inhibitor combination agents are not available: extended-infusion meropenem or imipenem/cilastatin therapy if MIC is ≤8 mcg/mL PLUS a second agent based on *in vitro* susceptibility results

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≤8 mcg/mL PLUS a second agent such as an aminoglycoside or a polymixin as determined by *in vitro* susceptibility data. This approach of the addition of an aminoglycoside or polymixin in combination with an extended-infusion carbapenem has a higher association with nephrotoxicity, and a growing number of studies indicate that these regimens are less effective than the more recently Food and Drug Administration-approved beta-lactams that target CRE. Therefore, use of more recently approved CRE-active agents is preferred for the treatment of CRE infections, when available.	

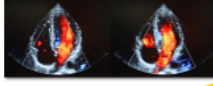|	
Pseudomonas Bacteremia SAY: When *Pseudomonas* species are growing in cultures, the microbiology lab initial report may indicate that blood cultures are growing with an oxidase positive, non-lactose-fermenting Gram-negative rod. As usual, it is important to determine the source, commonly pulmonary, catheter/hardware, urine, or wound, and obtain source control whenever possible. There are a limited number of commonly tested agents with activity against *Pseudomonas*: piperacillin/tazobactam, cefepime, ceftazidime, carbapenems (not ertapenem), fluoroquinolones (not moxifloxacin), and aminoglycosides. Data do not support the use of combination therapy over monotherapy for the treatment of *Pseudomonas* bacteremia when susceptibilities are available. There is no difference in cure rates or mortality in patients receiving beta-lactam monotherapy compared with combination therapy. However, except for pseudomonal urinary tract infections, aminoglycosides should not be used as monotherapy given evidence that aminoglycoside monotherapy is associated with worse outcomes than beta-lactam monotherapy. Consider obtaining an infectious diseases consult for assistance in managing infections caused by *Pseudomonas* isolates that are resistant to both beta-lactams and anti-pseudomonal fluoroquinolones. Most patients with pseudomonal bacteremia can be treated with 10–14 days of antibiotics. Oral options for *Pseudomonas* are ciprofloxacin and levofloxacin. If these agents are used for susceptible isolates, remember to use higher doses (750 orally twice daily for ciprofloxacin and 750 orally daily for levofloxacin in patients with normal renal function).	**Slide 13**

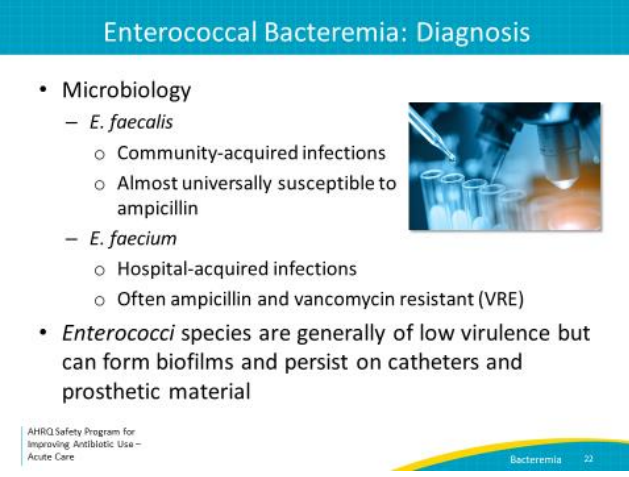| Slide Title and Commentary	Slide Number and Slide
Staphylococcus aureus **Bacteremia: Diagnosis** SAY: Let's move on to Gram-positive bacteria, beginning with *Staph aureus*. Because *Staph aureus* has very different risk factors, clinical presentations, treatment approaches, and outcomes in children versus adults, unlike all the other organisms discussed in this presentation, we will limit discussion of *Staph aureus* to the adult population. Determining the source of S*taph aureus* bacteremia and whether there has been metastatic spread are of critical importance. Based on history and physical exam, imaging should be obtained with particular emphasis on the spine exam, as concomitant vertebral osteomyelitis, discitis, and/or epidural abscesses are not uncommon.	**Slide 14** *Staphylococcus aureus* Bacteremia: Diagnosis • Determining the source of *S. aureus* bacteremia and whether there has been metastatic spread are of *critical* importance[15] • Based on history and physical exam, imaging should be obtained – Concomitant vertebral osteomyelitis/discitis/epidural abscesses are not uncommon AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 14

Staphylococcus aureus **Bacteremia: Diagnosis**
 	
SAY:
 	
All adult patients with *S. aureus* bacteremia should have echocardiography to assess for endocarditis. Transesophageal echo or TEE is more sensitive than transthoracic echo or TTE in detecting smaller vegetations; thus, most patients should have a TEE if the initial TTE does not show vegetations or if further definition of the cardiac anatomy is needed. TEE is particularly important in patients at low risk for endocarditis in whom short-course therapy is desired and patients at high risk for cardiac complications (e.g., prosthetic valves, permanent cardiac devices, cardiac conduction abnormalities, prolonged bacteremia or fevers) in whom surgical management may be required.
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	Staphylococcus aureus Bacteremia: Diagnosis[13]
	
	• All patients must have echocardiography to assess for endocarditis
	  – Transesophageal echocardiogram (TEE) is more sensitive than transthoracic echocardiogram (TTE) in detecting smaller vegetations[16]
	  – Most patients should receive TEE[15]
	    ○ Patients at low risk for endocarditis in whom short-course therapy is desired
	    ○ Patient at high risk for cardiac complications (e.g., prosthetic valves, permanent cardiac devices, cardiac conduction abnormalities, prolonged bacteremia or fever)
	
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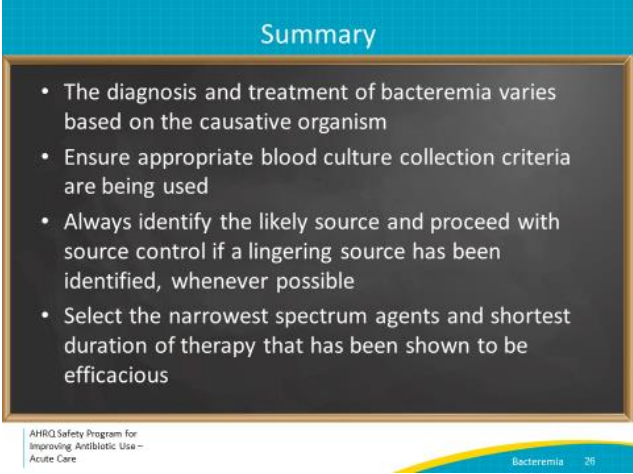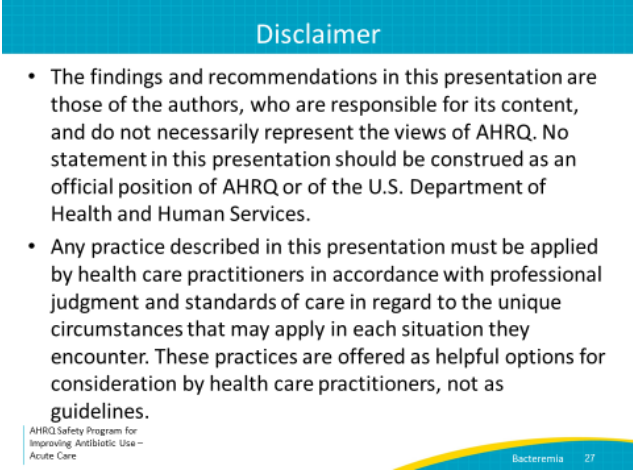| Slide Title and Commentary	Slide Number and Slide

***Staphylococcus aureus* Bacteremia: Management**
 	
SAY:
 	
In contrast to the management of most Gram-negative bloodstream infections, followup blood cultures should *always* be obtained to demonstrate clearance of *Staph aureus* bacteremia. Source control is essential. All removable devices should be removed and all abscesses should be debrided. Infectious diseases consultation has been demonstrated to improve outcomes in patients with *Staph aureus* bacteremia and should be obtained routinely.
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	Staphylococcus aureus Bacteremia: Management
	
	• Blood cultures should be obtained to demonstrate clearance of bacteremia[15]
	• Source control is *essential*
	  – Remove hardware
	  – Debride abscesses
	• Infectious diseases consultation[17]
	
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***Staphylococcus aureus* Bacteremia: Management**
 	
SAY:
 	
Uncomplicated *Staph aureus* bacteremia is defined as endocarditis excluded with a TEE (in select cases a very good quality TTE may suffice), no implanted prostheses, followup blood cultures are negative, the patient defervesces within 72 hours of initiating effective therapy, and the patient has no evidence of metastatic staphylococcal infection. Some clinicians always consider MRSA to indicate complicated infection because it can be more challenging to treat, although there are likely a subset of patients with MRSA bacteremia who can receive a 2-week course. All cases of *Staph aureus* bacteremia that do not meet this uncomplicated definition should be considered complicated.
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	Staphylococcus aureus Bacteremia: Management
	
	• Uncomplicated[15]
	  – Endocarditis excluded with a TEE
	    ○ In select cases a very good quality TTE suffices
	  – No implanted prosthetic devices
	  – Followup blood cultures are negative for *S. aureus*
	  – Patient defervesces within 72 hours of initiating effective therapy
	  – Patient has no localizing signs or symptoms of metastatic staphylococcal infection
	  – MSSA
	• Complicated
	  – All other cases
	
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Slide Title and Commentary	Slide Number and Slide
MSSA Bacteremia: Management SAY: Methicillin-susceptible *Staph aureus* or MSSA should be treated with anti-staphylococcal penicillins (such as oxacillin or nafcillin) or cefazolin. Cefazolin is associated with fewer side-effects, but patients with deep-seated infections may develop resistance. Vancomycin is associated with a higher failure rate than anti-staphylococcal beta-lactams and should not be used for convenience of dosing. Note that cefazolin can be dosed after hemodialysis without requiring a central catheter. Strongly consider desensitization for patients with serious penicillin allergies who cannot tolerate cephalosporins.	**Slide 18** **MSSA Bacteremia: Management** • MSSA should be treated with anti-staphylococcal penicillins (oxacillin, nafcillin) or cefazolin – Cefazolin is associated with fewer side effects but patients with deep-seated infections may develop resistance[18,19] – Vancomycin is associated with a higher failure rate and should not be used for convenience[20,21] – Strongly consider desensitization for patients with serious penicillin allergies who cannot tolerate cephalosporins AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 18
MRSA Bacteremia: Management SAY: Methicillin-resistant *Staph aureus* or MRSA should be treated with vancomycin or daptomycin. Vancomycin is still considered by many experts to be the agent of first choice. Daptomycin can be considered in patients with renal toxicity due to vancomycin or if the vancomycin MIC is > 1.5 mcg/mL. Although the U.S. Food and Drug Administration–approved dose of daptomycin for *S. aureus* bacteremia is 6 mg/kg, some infectious disease clinicians opt to use higher doses. If bacteremia persists despite source control for more than 5 to 7 days or if the patient is deteriorating clinically, salvage regimens may be required and should be determined in consultation with infectious diseases.	**Slide 19** **MRSA Bacteremia: Management** • Vancomycin still considered by most to be the agent of first choice[22] • Daptomycin can be considered in patients with renal toxicity due to vancomycin or if the vancomycin MIC is greater than 1.5 mcg/mL[23] – Higher doses recommended • If bacteremia persists despite source control for more than 5–7 days or if patient is deteriorating clinically, salvage regimens may be required AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 19

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S. aureus Bacteremia: Management SAY: The addition of gentamicin is not recommended for *Staph aureus* bacteremia or native-valve endocarditis. It is associated with nephrotoxicity in the absence of clinical benefit. The routine addition of rifampin is not recommended for *Staph aureus* bacteremia or native valve endocarditis. A randomized controlled trial showed no overall benefit with the addition of rifampin. Rifampin can be considered in consultation with infectious diseases specialists when the source of bacteremia is a prosthetic joint or spinal hardware. It should not be added until after blood cultures have cleared to reduce the risk of emergence of resistance. The addition of gentamicin and rifampin <u>is</u> recommended for prosthetic valve endocarditis due to *Staph aureus*.	**Slide 20** S. aureus Bacteremia: Management[18,20] • The addition of gentamicin is not recommended for *S. aureus* bacteremia or native valve endocarditis[22,24] – It is associated with nephrotoxicity in the absence of clinical benefit[25] • The routine addition of rifampin is not recommended for *S. aureus* bacteremia or native valve endocarditis[22,26] – Consider in consultation with infectious disease specialists when the source of bacteremia is a prosthetic joint or spinal hardware o Rifampin should not be initiated until after blood cultures have cleared • The addition of gentamicin and rifampin is recommended for prosthetic valve endocarditis[22] AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 20
S. aureus Bacteremia: Duration of Therapy SAY: All durations of therapy for *Staph aureus* bacteremia should be calculated from the day of the first negative blood culture or obtainment of source control, whichever is later. Uncomplicated *Staph aureus* bacteremia can be treated for 14 days. Complicated *Staph aureus* bacteremia should be treated for at least 28–42 days (42 days is the minimum for osteomyelitis). Right-sided endocarditis can be treated for 14 days in intravenous drug users with MSSA and minimal comorbidities, no hardware, no embolic disease other than septic pulmonary emboli, and if oxacillin or nafcillin is used. All other patients with right-sided infective endocarditis should receive 28–42 days. Left-sided endocarditis should be treated for 42 days (or more).	**Slide 21** S. aureus Bacteremia: Duration of Therapy • All durations should be calculated from the day of the first negative blood culture or obtainment of source control, whichever is later • Uncomplicated *S. aureus* bacteremia: 14 days • Complicated *S. aureus* bacteremia: 28–42 days – Osteomyelitis: 42 days at a minimum • Right-sided endocarditis – Injecting drug users with MSSA and minimal comorbidities, no hardware, no embolic disease other than septic pulmonary emboli: 14 days oxacillin/nafcillin – Everyone else: 28–42 days • Left-sided endocarditis: 42 days (or more) AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 21

Slide Title and Commentary	Slide Number and Slide
Enterococcal Bacteremia: Diagnosis SAY: The two most common species of *Enterococci* are *E. faecalis* and *E. faecium*. Of these two, *E. faecalis* is more common. *E. faecalis* is a community-acquired pathogen, and is almost universally susceptible to ampicillin, which is the agent of choice. *E. faecium* is more often seen in hospital-acquired infections, is often resistant to ampicillin, and can be vancomycin-resistant, referred to as VRE. *Enterococci* are of relatively low virulence but have two features that contribute to their pathogenicity. They can be difficult to treat due to intrinsic and acquired resistance to several antibiotic classes and have the ability to form biofilms that can persist on catheters and prosthetic material.	**Slide 22**

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Enterococcal Bacteremia: Diagnosis
 	
SAY:
 	
Enterococci growing in the blood fall into four general categories. First, they can be contaminants (likely from the skin). Treatment is not needed for contaminants. Second, they can cause bacteremia from translocation in a patient post-procedure (usually a biliary procedure or urinary procedure) or from gut disruption (such as with mucositis). These reasons for enterococcal bacteremia generally lead to transient bacteremia and can be treated with a short course of therapy (4–5 days).
 	
Third, *Enterococcus* bacteremia can also be the result of an infected source, commonly a urinary tract infection, prostatitis, or a biliary tract infection. These may require a longer course of therapy to address the primary source (at least 7 days; longer for prostatitis). Finally, enterococci can cause endocarditis which requires prolonged therapy (4–6 weeks). Consider endocarditis in settings of persistent bacteremia, prosthetic valves, or in patients with other presentations consistent with endocarditis such as persistent fevers, fatigue, and malaise.
 	
Unless endocarditis is suspected, the patient has endovascular hardware, or signs and symptoms persist, there is a limited role for followup blood cultures if the source is known.
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	### Enterococcal Bacteremia: Diagnosis
	
	• *Enterococcus* growing in the blood falls into four general categories
	  1. Contaminant (likely from skin)
	  2. Bacteremia from translocation in a patient post-procedure (usually biliary) or with gut disruption (e.g., mucositis)
	  3. Bacteremia related to an infected source: commonly UTI/prostatitis and biliary tract infection
	  4. Endocarditis[27]
	    o Consider in settings of persistent bacteremia, prosthetic valves, or presentations consistent with endocarditis
	• Source control whenever possible
	• Minimal role for followup blood cultures if source is known and controlled
	
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Slide Title and Commentary	Slide Number and Slide

E. faecalis Bacteremia: Management
 	
SAY:
 	
First-line therapy for _E. faecalis_ is ampicillin. Vancomycin is used for patients with severe penicillin allergy. Neither of these agents are bactericidal for this organism; however, combination therapy with either gentamicin or ceftriaxone is bactericidal. Combination therapy is clearly needed for endocarditis; failure rates reach up to 40 percent without it. However, there is no evidence that combination therapy is needed for other infections including bloodstream infections or prosthetic joint infection. Infectious diseases consultation is strongly recommended for the management of endocarditis due to _E. faecalis._
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	E. faecalis Bacteremia: Management
	• Ampicillin (1st line) and vancomycin (2nd line) are not bactericidal
	  – Combination therapy with gentamicin is bactericidal
	  – Newer data suggest combination of ampicillin and ceftriaxone is bactericidal
	• When is combination therapy needed?[28,29]
	  – Endocarditis: yes ✓
	    o Failure rates up to 40% with monotherapy
	    o 4–6 weeks of IV therapy
	  – Other infections: no evidence of benefit ✗
	• Infectious diseases consultation is recommended for endocarditis due to _E. faecalis_
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E. faecium Bacteremia: Management SAY: Treatment of _E. faecium_ bacteremia can be challenging. If susceptible, ampicillin is the agent of first choice (or vancomycin for severe penicillin allergy). However, many isolates are resistant to both ampicillin and vancomycin. Linezolid and daptomycin are the most commonly used agents for bacteremia due to VRE. Infectious diseases consultation is strongly recommended for management of VRE bacteremia <u>or</u> endocarditis to assist with optimal antibiotic selection.	**Slide 25** _E. faecium_ Bacteremia: Management • Treat with ampicillin or vancomycin if susceptible • Treat with linezolid or daptomycin if _not_ susceptible to ampicillin or vancomycin • Infectious diseases consult recommended for VRE bacteremia _or_ endocarditis AHRQ Safety Program for Improving Antibiotic Use – Acute Care Bacteremia 25

Slide Title and Commentary	Slide Number and Slide
Summary SAY: In conclusion, the diagnosis and treatment of bacteremia varies based on causative organism. It is important that appropriate blood culture collection criteria are used. Always identify the likely source of bacteremia and proceed with source control whenever possible if a lingering source has been identified. Finally, select the narrowest spectrum agents and the shortest duration of therapy that has been shown to be efficacious.	**Slide 26** Summary • The diagnosis and treatment of bacteremia varies based on the causative organism • Ensure appropriate blood culture collection criteria are being used • Always identify the likely source and proceed with source control if a lingering source has been identified, whenever possible • Select the narrowest spectrum agents and shortest duration of therapy that has been shown to be efficacious AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 26
Disclaimer SAY: The findings and recommendations in this presentation are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this presentation should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services. Any practice described in this presentation must be applied by health care practitioners in accordance with professional judgment and standards of care in regard to the unique circumstances that may apply in each situation they encounter. These practices are offered as helpful options for consideration by health care practitioners, not as guidelines.	**Slide 27** Disclaimer • The findings and recommendations in this presentation are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this presentation should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services. • Any practice described in this presentation must be applied by health care practitioners in accordance with professional judgment and standards of care in regard to the unique circumstances that may apply in each situation they encounter. These practices are offered as helpful options for consideration by health care practitioners, not as guidelines. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 27

Slide Title and Commentary	Slide Number and Slide
References	**Slide 28** References 1. Towns ML, Jarvis WR, Hsueh PR. Guidelines on blood cultures. J Microbiol Immunol Infect. 2010 Aug;43(4):347-9. PMID: 20688297. 2. Lee A, Mirrett S, Reller LB, et al. Detection of bloodstream infections in adults: how many blood cultures are needed? J Clin Microbiol. 2007 Nov;45(11):3546-8. PMID: 17881544. 3. 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* bacteria. JAMA Intern Med. 2019 Jan 22. [Epub ahead of print] PMID: 30667477. 4. Chotiprasitsakul D, Han JH, Cosgrove SE, et al. Comparing the outcomes of adults with *Enterobacteriacea* bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. Clin Infect Dis. 2018 Jan 6;66(2):172-7. PMID: 29190320. 5. Yahav D, Franceschini E, Koppel F, et al. Seven versus fourteen days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a non-inferiority randomized controlled trial. Clin Infect Dis. 2018 Dec 11. [Epub ahead of print] PMID: 30535100. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 43
References	**Slide 29** References 6. Canzoneri CN, Akhavan BJ, Tosur Z, et al. Follow-up blood cultures in Gram-negative bacteremia: are they needed? Clin Infect Dis. 2017 Nov;65(11):1776-9. PMID: 29020307. 7. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-Day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018 Sep;320(10):984-94. PMID: 30208454. 8. Tamma PD, Girdwood SC, Gopaul R, et al. The use of cefepime for treating AmpC β-lactamase-producing *Enterobacteriaceae*. Clin Infect Dis. 2013 Sep;57(6):781-8. PMID: 23759352. 9. Siedner MJ, Galar A, Guzmán-Suarez BB, et al. Cefepime vs other antibacterial agents for the treatment of *Enterobacter* species bacteremia. Clin Infect Dis. 2014 Jun;58(11):1554-63. PMID: 24647022. 10. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012-2013. JAMA. 2015 Oct;31(14):1479-87. PMID: 26436831. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 44
References	**Slide 30** References 11. Morrill HJ, Pogue JM, Kaye KS, et al. Treatment options for carbapenem-resistant *Enteriobacteriaceae* infections. Open Forum Infect Dis. 2015 May;2(2):ofv050. PMID: 26125030. 12. Kaye KS, Pogue JM. Infections caused by resistant Gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015 Oct;35(10):949-62. PMID: 26497481. 13. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant *Enterobacteriaceae* infections: The TANGO II randomized clinical trial. Infect Dis Ther. 2018 Dec;7(4):439-55. PMID: 30270406. 14. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Clin Infect Dis. 2019 Jan 18;68(3):355-64. PMID: 29893802. 15. Cosgrove SE, Fowler VG Jr. Optimizing therapy for methicillin-resistant *Staphylococcus aureus* bacteremia. Semin Respir Crit Care Med. 2007 Dec;28(6):624-31. PMID: 18095226. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 45

Slide Title and Commentary	Slide Number and Slide
References	**Slide 31** **References** 16. Reynolds HR, Jagen MA, Tunick PA, et al. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr. 2003 Jan;16(1):67-70. PMID: 12514637. 17. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation of quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: results from a large multicenter cohort study. Clin Infect Dis. 2015 May 15;60(10):1451-61. PMID: 2501854. 18. Li J, Echevarria KL, Hughes DW, et al. Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible *Staphylococcus aureus*. Antimicrob Agents Chemother. 2014 Oct;58(10):5117-24. PMID: 24936596. 19. Lee S, Choe PG, Song KH, et al. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia? Antimicrob Agents Chemother. 2011 Nov;55(11):5122-6. PMID: 21825299. 20. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore). 2003 Sep;82:333-9. PMID: 14530782. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 46
References	**Slide 32** **References** 21. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2007 Jan;44(2):190-6. PMID: 17173215. 22. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011 Feb;52(3): e18-55. PMID: 21208910. 23. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006 Aug;355(7): 653-65. PMID: 16914701. 24. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015 Oct;132(15):1435-86. PMID: 26373316. 25. Cosgrove SE, Vigliani GE, Fowler VG, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis. 2009 Mar;48(6):713-21. PMID: 19207079. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 47
References	**Slide 33** **References** 26. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomized, double-blind, placebo-controlled trial. Lancet. 2018 Feb;391(10121):668-78. PMID: 29249276. 27. Anderson DJ, Murdoch DR, Sexton DJ, et al. Risk factors for infective endocarditis in patients with *Enterococcal* bacteremia: a case-control study. Infection. 2004 Apr;32(2):72-7. PMID: 15057570. 28. Beganovic M, Luther MK, Rice LB, et al. A review of combination therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. Clin Infect Dis. 2018 Jul 2;67(2):303-9. PMID: 29390132. 29. Graninger W, Ragette R. Nosocomial bacteremia due to *Enterococcus faecalis* without endocarditis. Clin Infect Dis. 1992 Jul;15(1):49-57. PMID: 1617073. AHRQ Safety Program for Improving Antibiotic Use – Acute Care — Bacteremia 48