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Follow-up blood cultures are often needed after bacteremia

Bacteremia is common and associated with significant morbidity and mortality. Bloodstream infections rank among the leading causes of death in North America and Europe.[1]

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In this issue, Mushtaq et al[2] contend that follow-up blood cultures after initial bacteremia are not needed for most hospitalized patients. Not repeating blood cultures after initial bacteremia has been proposed to decrease hospitalization length, consultations, and healthcare costs in some clinical settings. However, without follow-up cultures, it can be difficult to assess the adequacy of treatment of bacteremia and associated underlying infections.

GRAM-NEGATIVE ORGANISMS

Results of retrospective studies indicate that follow-up cultures may not be routinely needed for gram-negative bacteremia. In a review by Canzoneri et al of 383 cases with subsequent follow-up cultures,[3] 55 (14%) were positive. The mean duration of bacteremia was 2.8 days (range 1 to 15 days). Of the 55 persistently positive blood cultures, only 8 (15%) were caused by gram-negative organisms. Limitations to this study included the lack of patient outcome data, a low event rate, and the retrospective design.[4]

In a retrospective case-control study of follow-up cultures for 862 episodes of *Klebsiella pneumoniae* bacteremia,[5] independent risk factors for persistent bacteremia were intra-abdominal infection, higher Charlson comorbidity index score, solid-organ transplant, and unfavorable treatment response.

These studies confirm that persistent bacteremia is uncommon with gram-negative organisms. They also support using comorbidities and treatment response to guide the ordering of follow-up blood cultures.

WHEN IS FOLLOW-UP CULTURE USEFUL?

Although follow-up blood cultures may not be needed routinely in patients with gram-negative bacteremia, it would be difficult to extrapolate this to gram-positive organisms, especially *Staphylococcus aureus*.

In Canzoneri et al,[3] 43 (78%) of the 55 positive follow-up cultures were due to gram-positive organisms. Factors associated with positive follow-up cultures were concurrent fever, presence of a central intravenous line, end-stage renal disease on hemodialysis, and diabetes mellitus. In addition, infectious disease consultation to decide the need for follow-up cultures for *S aureus* bacteremia has been associated with fewer deaths, fewer relapses, and lower readmission rates.[6,7]

Without follow-up cultures, assessing the adequacy of bacteremia treatment and associated underlying infections can be difficult

In certain clinical scenarios, follow-up blood cultures can provide useful information, such as when the source of bacteremia is endocarditis or cardiac device infection, a vascular graft, or an intravascular line. In the Infectious Diseases Society of America guidelines for diagnosis and management of catheter-related bloodstream infections, persistent or relapsing bacteremia for some organisms is a criterion for removal of a long-term central venous catheter.[8]

Follow-up cultures are especially useful when the focus of infection is protected from antibiotic penetration, such as in the central nervous system, joints, and abdominal or oth-

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er abscess. These foci may require drainage for cure. In these cases or in the setting of unfavorable clinical treatment response, follow-up blood cultures showing persistent bacteremia can prompt a search for unaddressed or incompletely addressed foci of infection and allow for source control.

The timing of follow-up cultures is generally 1 to 2 days after the initial culture. Although Mushtaq et al propose a different approach, traditional teaching has been that the last blood culture should not be positive, and this leads to ordering follow-up blood cultures until clearance of bacteremia is documented.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Repeating blood cultures after initial bacteremia: When and how often?

A: Repeat cultures are indicated in specific scenarios, but for most patients, frequent and indiscriminate repetition after an initial positive culture is unnecessary and may be associated with excessive use of resources. Prospective studies and practice guidelines are needed to help further define the indications.

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THE TENDENCY TO REPEAT CULTURES

Current literature lacks strong evidence for repeating previously positive blood cultures collected appropriately—ie, 10 mL of blood for aerobic culture and 10 mL for anaerobic culture from 2 different sites, and a positive result from both sets. However, because of the risk of serious complications of bacteremia, particularly in critically ill patients, many clinicians order multiple, repeated sets of blood cultures.

Tabriz et al[1] found that one-third of hospitalized patients got repeat cultures after an initial set, regardless of the result of the first set. Most (83.4%) of those cultures yielded no growth, 9.1% grew the same pathogen, and 5.0% were contaminated. Finding a new pathogen was rare, occurring in only 2.5% of repeated cultures.

Wiggers et al[2] reported an even higher number of repeat cultures ordered for patients who had an initially positive culture: 38.9%.[2] And in another study,[3] half of the patients received more than 2 consecutive cultures.

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Drawbacks

Unrestrained ordering of repeat blood cultures can increase the risk of a false-positive result, leading to more cultures, echocardiography, other imaging tests, and unnecessary antimicrobial therapy, all of which puts patients at risk of adverse effects of treatment and missed alternative diagnoses and increases the length and cost of hospitalization.[4]

Advantages

On the other hand, repeat blood cultures may increase the diagnostic yield for conditions such as infective endocarditis and may have implications for the duration of antibiotic therapy.[1] The duration of therapy for bacteremia is usually determined from the last negative culture; hence, documenting clearance of bacteremia can determine a precise end-date for antibiotic therapy.

Bacteremia due to *Staphylococcus aureus* and to endovascular and epidural sources has been found to be independently associated with persistent bacteremia, detected in 6.6% of 1,801 index cases of bacteremia in a retrospective cohort study.[2] An endovascular source (adjusted odds ratio [OR] 7.66, 95% confidence interval [CI] 2.30–25.48), an epidural source (adjusted OR 26.99, 95% CI, 1.91–391.08), and *S aureus* bacteremia (adjusted OR 4.49, 95% CI 1.88–10.73) were independently associated with persistent bacteremia. *Escherichia coli* (5.1%, $P = .006$), viridans group streptococci (1.7%, $P = .035$), and beta-hemolytic streptococci (0%, $P = .028$) were associated with a lower likelihood of persistent bacteremia. Patients with persistent bacteremia were less likely to have achieved source control within 48 hours of the index event (29.7% vs 52.5%, $P < .001$).[2]

Repeat cultures are warranted for *S aureus* bacteremia regardless of methicillin susceptibility

WHEN REPEATING CULTURES IS APPROPRIATE

Repeating blood cultures after an initial positive result is superfluous, except in certain situations.

Suspected endovascular infection

Patients with endocarditis, thrombophlebitis, an indwelling device for epidural access, or a cardiovascular implantable electronic device should have repeat cultures after an initial positive culture. Implantable electronic device infection is suspected in the following cases: sustained positive blood culture (> 24 hours); relapsing bacteremia despite a course of appropriate antibiotic therapy; presence of an implantable cardioverter defibrillator; presence of a prosthetic cardiac valve; and an episode of bacteremia within 3 months of device placement.[5]

S aureus bacteremia

Repeat blood culture is warranted for *S aureus* bacteremia regardless of methicillin susceptibility.[1] But persistent methicillin-resistant *S aureus* (MRSA) bacteremia changes the management of these patients.[6] For example, the source of infection should be identified, followed by debridement or drainage, and then either high-dose or combination antimicrobial therapy.[6] Infective endocarditis from persistent MRSA bacteremia is an indication for surgery.[6]

Persistent *S aureus* bacteremia may change the duration of therapy, as the common practice is to continue treating uncomplicated gram-positive bacteremia for 14 days from the date of the first negative culture. Infection leading to infective endocarditis increases the duration of antibiotic therapy to at least 4 weeks.

Candidemia is an absolute indication for repeat blood culture

Candidemia

Candidemia is an absolute indication for repeat blood culture.[7] Patients with persistent candidemia should undergo imaging of the genitourinary tract, liver, and spleen as part of the evaluation for a deep-tissue source of infection.[7] Also, if the patient is initially treated with an echinocandin, therapy can be transitioned to fluconazole if the isolate is azole-susceptible, the patient's condition is clinically stable, and repeat cultures are negative.[7] Therefore, repeating cultures has therapeutic implications.

Confirming response to therapy

In patients with infective endocarditis or other endovascular infection caused by *S aureus*, *Enterococcus* species, or gram-negative bacilli,[1] repeat blood culture should be done to confirm therapeutic response. Patients with infective endocarditis whose condition is stable can be discharged to receive outpatient parenteral antibiotic therapy. However, patients with uncontrolled heart failure, systemic emboli, abscess, persistent fever, or persistently positive cultures are not candidates for outpatient therapy and require repeat cultures.[8]

Multidrug-resistant gram-negative bacilli

Bacteremia due to multidrug-resistant gram-negative bacilli requires repeat blood cultures to document clearance of bacteremia and to ensure the efficacy of antibiotics, as these organisms pose a higher risk of treatment failure, and combination synergistic regimens may be needed if bacteremia does not clear.

Febrile neutropenia

Blood cultures are important in the management of febrile neutropenia. In a study by Rosenblum et al,[9] repeat cultures were positive in 10.9% of patients with febrile neutropenia after an initial negative culture, but many of those organisms were of low pathogenicity, and a significant proportion were coagulase-negative staphylococci.[10] Another study showed that the frequency of detecting new pathogens by repeat culture in recurrent febrile neutropenia was higher than that in persistent febrile neutropenia (8% vs 2%) (P = .0491); a history of recent bacteremia was identified as a significant predictor of positive culture in recurrent febrile neutropenia.[11]

Persistent or new infection

Persistence of fever, leukocytosis, or other signs of infection 72 hours after appropriate antibiotic therapy is started requires follow-up blood cultures.

New episode of sepsis. A new episode of sepsis should be confirmed[12] using the systemic inflammatory response syndrome criteria, the newer definition of Sepsis-related Organ Failure Assessment (SOFA) in the intensive-care

unit, or the quick SOFA in general units. If the patient develops new signs of sepsis after response to treatment for initial bacteremia, repeat blood cultures should be considered.

Central line-associated bloodstream infection requires repeat cultures.[13] Persistence of bacteremia in this type of infection extends the duration of therapy, as most clinicians determine treatment duration from the last negative culture. Persistent bacteremia also influences the decision to salvage or remove the catheter. Microbiologic clearance of bacteremia on blood culture can also guide the time of reinsertion if the catheter was removed.

Concern for an unresolved focus of infection such as abscess, joint infection, or retained catheter is an indication for repeat blood cultures.

Bacteremia of unknown source. In clinical practice, we encounter scenarios in which blood cultures are positive but no source can be identified. In those situations, it is important to repeat blood cultures to document clearance. If bacteremia persists, we need to continue searching for the source.

WHEN ROUTINELY REPEATING CULTURES IS NOT INDICATED

Repeat blood cultures are not routinely indicated in patients with streptococcal bacteremia, uncomplicated gram-negative bacteremia, and bacteremia associated with localized infection such as cellulitis, community-acquired pneumonia, or pyelonephritis.[2,4] A study of patients with gram-negative bacteremia found that 17 repeated cultures needed to be drawn to yield 1 positive culture.[14]

Isolated fever or leukocytosis does not accurately predict bacteremia.[4] A study that excluded neutropenic and intensive-care patients reported none of the initially negative cultures to be positive when repeated.[15]

Ordering repeat cultures in response to persistent fever is a common practice, even though fever is typical in the first 72 hours of antibiotic therapy. Such cultures rarely if ever reveal new pathogens, and results can be predicted based on cultures before the start of antibiotics.[15] For patients on antibiotics, physicians should therefore wait for results of the preantibiotic cultures rather than order new cultures in response to persistent fever.[15]

WOULD WE MISS PERSISTENT BACTEREMIA?

In theory, not repeating blood cultures could miss persistent bacteremia, but this is unlikely if the concerns discussed above are considered. Further, persistent bacteremia would result in clinical signs and symptoms that should prompt repeat cultures.

FREQUENCY OF REPEAT BLOOD CULTURES

There are no evidence-based guidelines for the frequency of repeating cultures. The Infectious Diseases Society of America recommends repeating blood cultures 2 to 4 days after the index positive culture in the case of multidrug-resistant *S aureus* bacteremia, and every day or every other day for candidemia.[6,7,9]

A study evaluating the practice patterns of repeating cultures after an initial bacteremia showed that 34.7% were done within 24 hours and 44.7% were done in 2 to 4 days.[1] There is no evidence that repeating blood cultures daily is necessary in these patients. As a general rule, it should be done 48 to 72 hours after a positive culture.

There are no evidence-based guidelines for the frequency of repeating cultures

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