The Clinical Importance of Microbiological Findings in the Diagnosis and Management of Bloodstream Infections

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Bloodstream infections are associated with high morbidity and mortality. Accurate identification of blood isolates to the species level and identification of the source of infection and/or the portal of entry are crucial for optimal management of these infections. These investigations—in addition to clinical findings and laboratory and imaging studies—are central to informing and directing efficient and effective diagnostic examinations and to choosing the optimal antimicrobial regimen. Four case studies that demonstrate the importance of identifying the causative agents and the source of infection are discussed to illustrate the central importance of microbiological findings in the diagnosis of bacteremia and bloodstream infections associated with infections at other sites.

Bloodstream infections (BSIs) are associated with high morbidity and mortality. In the United States, an estimated 250,000 patients develop bacteremia or fungemia every year. Many infections are acquired in hospitals [1]. Rates of mortality associated with BSI in the United States have been estimated to be 16%–40% [2]. The importance of early antimicrobial therapy is demonstrated by studies showing that survival of patients with sepsis depends on early administration of adequate empirical antimicrobial therapy [3–5]. Among patients with BSI, attributable mortality is ~20% for patients treated with appropriate empirical therapy, compared with 34% for patients treated with inappropriate empirical therapy [3]. In addition to emphasizing the value of early empirical therapy, it is important to ensure that BSIs are diagnosed accurately and that infecting pathogens, their antimicrobial susceptibilities, and the possible primary sources of infection are evaluated thoroughly, to enable optimal targeted antimicrobial therapy.

Blood cultures and their microbiological analysis are essential for the diagnosis of BSI [1, 6, 7]. Although it has been generally regarded that 2 or 3 blood cultures are sufficient to confirm almost all BSIs, recent research has shown that 2 blood cultures performed in a 24-h period will detect only 90% of BSIs in adults, and as many as 4 blood cultures may be needed to detect >99% of BSIs [8, 9].

Differentiation between primary and secondary BSIs and identification of nonvascular sources of infection may require culture and analysis of samples obtained from other body sites, such as respiratory tract, pleural fluid, wound swab, bone and tissue biopsy, and CSF specimens. Qualitative and quantitative microbiological results for these samples may help to establish the clinical significance of bacteremia and can provide clues to the likely presence and location of underlying sources of infections, which may not always be apparent from the clinical presentation. Microbiological findings from distant sites, such as a psoas abscess, obtained at a later stage in the course of a BSI may indicate that a complication has arisen from hematogenous seeding.

The nonmicrobiological procedures used to inves-
tigate deep-seated sources of BSI include radiography, trans-thoracic and transesophageal echocardiography, CT, positron emission tomography, and MRI. Laboratory investigations, including WBC count, C-reactive protein level measurement, and possibly, procalcitonin level measurement, may help to evaluate the clinical course and severity of infectious disease. Identification of the underlying source of infection is essential for implementation of adequate treatment, including surgical intervention when appropriate. Treatment that clears a BSI but leaves an undiagnosed, underlying source is unlikely to be successful in the medium-to-long term and may delay effective therapy for a life-threatening complication.

In a landmark study conducted in the early 1990s in the United States by Weinstein et al. [10], 843 episodes of bacteremia and fungemia were analyzed for their portal of entry. BSIs were considered to be primary in 44.7% of cases; in 19.1% of cases, an intravascular catheter was the source of infection, and 25.6% of cases had an unknown portal of entry. The most frequent secondary sources were the genitourinary tract (17.4%), the respiratory tract (12.3%), the abdomen (12.1%), and the skin and skin structure (6.3%) [10]. In an analysis of 111 patients with BSI in French hospitals, 29% had primary infections without a defined source, 26% had catheter-related infections, and 45% had infection secondary to other sources [11]. Although colonized (“infected”) catheters are the most frequently identified source, infection at numerous other sites can also cause BSIs. For example, in a prospective study involving patients from 2 US hospitals, catheters were the source of infection in 26% of nosocomial BSI episodes, whereas the source was described as genitourinary in 14%, gastrointestinal or biliary in 13%, respiratory in 9%, and skin or soft tissue in 4% (table 1) [12]. The distribution of sources of BSIs was broadly similar for community-onset infections [12].

For the diagnosis of BSIs related to intravascular devices, a meta-analysis of 51 studies revealed that paired quantitative blood cultures were the most accurate diagnostic test, whereas other methods, such as catheter-segment culture and acridine orange leukocyte cytospin, also had acceptable sensitivity, specificity, and negative predictive value [13]. Determination of the differential time to positive results of cultures of blood obtained via a central venous catheter versus peripheral blood cultures is another relatively new method for the diagnosis of catheter-related BSIs; this method correlates well with quantitative blood cultures and makes use of routine continuous blood culture monitoring for positivity. A diagnosis of catheter-related BSI requires the semiautomated blood culture system to detect a positive result for the central venous catheter blood sample at least 2 h earlier than it detects a positive result for the peripheral blood sample [14].

Several approaches have been examined to reduce the time to microbial species identification in the diagnosis of BSI, including PCR-based methods and fluorescence in situ hybridization for direct species identification of isolates from microscopically positive blood cultures [15, 16], as well as PCR techniques to directly identify methicillin-resistant Staphylococcus aureus from blood cultures showing gram-positive cocci in clusters [17]. Methods for the direct identification of microbial DNA from blood by various amplification methods are currently being developed, but their review is beyond the scope of this article.

**DEFINITIONS OF BACTEREMIA AND BSI**

Bacteremia is defined as the presence of viable microorganisms in the bloodstream and can be categorized as transient, intermittent, or persistent (figure 1) [6]. Transient bacteremia lasts for minutes or a few hours and most frequently occurs after manipulation of nonsterile body sites—for example, during

<table>
<thead>
<tr>
<th>Source of infectiona</th>
<th>Nosocomial BSI (n = 218)</th>
<th>Community-onset BSI (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter</td>
<td>57 (26)</td>
<td>43 (26)</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>31 (14)</td>
<td>32 (19)</td>
</tr>
<tr>
<td>Gastrointestinal or biliary tract</td>
<td>27 (13)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>20 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>SSTI</td>
<td>9 (4)</td>
<td>15 (9)</td>
</tr>
</tbody>
</table>

**NOTE.** SSTI, skin and soft-tissue infection. Source: Diekema et al. [12].

* a Sources are for culture-confirmed cases.
dental procedures; after gastrointestinal biopsy; after percutaneous catheterization of the vascular system, bladder, or common bile duct; and after surgical debridement or drainage—that is, after procedures involving contaminated or colonized skin and/or mucosal surfaces are performed and also at the onset of acute bacterial infections. Intermittent bacteremia is defined as bacteremia due to the same microorganism that is detected intermittently in the same patient because of a cycle of clearance and recurrence. Intermittent bacteremia is often associated with undrained closed-space infections, such as intra-abdominal or soft-tissue abscesses, and may also occur in patients with liver abscesses, cholangitis, and focal infections, including pneumonia, osteomyelitis, and spondylodiscitis. Persistent bacteremia is a characteristic of infective endocarditis (IE) [18] and other intravascular infections, such as vascular-graft infection, a mycotic aneurysm, or an infected thrombus. Persistent bacteremia also occurs during the early stages of systemic bacterial infections, such as brucellosis and typhoid fever.

According to the Centers for Disease Control and Prevention (CDC), BSI can be defined as the presence of viable bacteria in the blood (i.e., bacteremia) documented by a positive blood culture result [19]. Primary BSI (i.e., a BSI without a documented primary source of infection) can be distinguished from secondary BSI (i.e., a BSI secondary to a localized focus of infection, such as pneumonia, biliary tract infection, skin and soft-tissue infection, and wound infection).

The CDC surveillance definitions divide primary BSIs into laboratory-confirmed BSIs and clinical sepsis [20]. A diagnosis of laboratory-confirmed BSI is made if at least 1 of 2 criteria is met. First, the patient must have a recognized pathogen cultured from ≥1 blood specimen, and the cultured organism must not be related to an infection at another site. Second, the patient must have fever, chills, or hypotension and at least 1 of the following: (1) a common skin contaminant (e.g., diphtheroids, Bacillus species, Propionibacterium species, coagulase-negative staphylococci, or micrococci) isolated from ≥2 blood cultures drawn on separate occasions; (2) a common skin contaminant, as defined above, isolated from at least 1 blood culture from a patient with an intravascular line and for whom the physician institutes appropriate antimicrobial therapy; or (3) a positive result of antigen testing of blood (e.g., positive for Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, or group B streptococcus) and signs and symptoms with positive laboratory results that are not related to an infection at another site. Similar criteria were suggested for patients aged ≤1 year.

The CDC-approved diagnosis of clinical sepsis requires the presence of at least 1 of the following clinical signs or symptoms with no other recognized cause—temperature >38°C, hypotension, or oliguria—and the presence of all of the following conditions: blood culture was not performed, or no organisms or antigen were detected in blood; there was no apparent infection at another site; and the physician initiated treatment for sepsis. Again, slightly modified criteria were suggested for children aged ≤1 year.

With these definitions in mind, the following case studies illustrate the central importance of microbiological findings in the diagnosis of both bacteremia and BSI associated with infection at other sites. A thorough understanding of laboratory and clinical microbiology is required both to direct microbiological investigations and to interpret the findings accurately. Microbiological findings may also guide the use of other approaches to the diagnosis and treatment of infectious diseases and their underlying illnesses, because bacteremia may be the first clue to a serious underlying disease, such as HIV infection or hematological or solid-organ malignancy.

**CASE STUDY 1**

A 64-year-old woman presented to an outpatient clinic in August 2005 with recurrent fever; her temperature had reached 39.5°C up to 3 times per week in the past 3 years. She was a smoker with chronic obstructive pulmonary disease and peripheral artery disease, had undergone aortoiliac bypass graft surgery in 1993, and had an abscess of the right leg of unknown etiology in 2001. Initial diagnostic evaluation on an outpatient basis revealed no significant findings, but 1 of 8 sets of blood cultures obtained over a 5-day observation period was positive for Streptococcus anginosus. The patient was hospitalized, and
an exhaustive clinical, laboratory, and imaging evaluation was performed, including abdominal ultrasound and transesophageal echocardiography, the findings of which were all negative. During the 7-day hospital stay, all results of follow-up blood cultures performed daily were negative until the day before the patient's scheduled discharge, when there was another blood culture positive for *S. anginosus*. Antimicrobial treatment was initiated with 10 mIU of penicillin G administered intravenously 3 times per day for 4 weeks, which resulted in an apparent complete recovery and no additional positive blood culture results.

Imaging studies were intensified to find a primary focus of infection. Findings of transesophageal echocardiography were repeatedly negative, revealing no evidence of vegetations on the valves or signs of IE. Findings of bone scan and magnetic resonance tomography of the spine were also negative, with no evidence of vertebral osteomyelitis. Whole body CT and a leukocyte scan revealed no abnormal findings suggestive of an occult abscess. Discharge from the hospital was postponed pending the results of further investigations to find an underlying source of infection. Finally, an 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography scan revealed signs suggestive of a chronic infection associated with the patient's aortoiliac bypass graft (figure 2). This finding was supported by the results of an additional abdominal CT scan. Vascular surgery revealed an infected aortobifemoral bypass graft with a green and yellow discoloration suggestive of duodenal leakage resulting from a retrodudodenal pressure ulcer (figure 3). The vascular prosthesis was removed and replaced, and no additional complications have been observed.

Although this patient with documented and apparent primary streptococcal bacteremia was treated using standard therapy and was observed to recover promptly, the recurrence of *S. anginosus* bacteremia, in the context of a history of recurrent fever, pointed to a deep-seated source of underlying infection that required a thorough diagnostic examination in addition to prolonged antimicrobial therapy. This approach resulted in a life-saving surgical intervention.

This case study illustrates the potential dangers of misdiagnosing a primary BSI when bacteremia resolves spontaneously or with treatment. If this patient had been discharged from the hospital after the apparent initial recovery, the source of infection would not have been identified, and a life-threatening condition might have been overlooked. This example shows that, in some cases, the diagnosis of BSI and its underlying primary source of infection may require more than the recommended 2 or 3 sets of blood cultures. In addition, if the patient is clinically stable, the clinician may consider delaying antimicrobial therapy and obtaining follow-up blood cultures to permit documentation of intermittent or persistent bacter-

### Table 2. Diagnostic implications of bacterial species identified from blood cultures.

<table>
<thead>
<tr>
<th>Species</th>
<th>Implications and/or underlying infectious disease</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>IE and vertebral osteomyelitis</td>
<td>[22, 23]</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>Device-related BSI and IE</td>
<td>[24, 25]</td>
</tr>
<tr>
<td><em>Streptococcus anginosus</em></td>
<td>Abscess (brain, lung, liver, or gastrointestinal)</td>
<td>[26, 27]</td>
</tr>
<tr>
<td><em>Streptococcus sanguinis</em></td>
<td>IE</td>
<td>[28]</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
<td>IE</td>
<td>[29–31]</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>IE, urinary tract infection, and intra-abdominal source</td>
<td>[32, 33]</td>
</tr>
<tr>
<td><em>Clostridium septicum</em></td>
<td>Fatal sepsis in immunocompromised patients</td>
<td>[34]</td>
</tr>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>Melioidosis</td>
<td>[35]</td>
</tr>
<tr>
<td><em>Salmonella enteritidis</em></td>
<td>Gastrointestinal tract infection and extraintestinal focus of infection, such as osteomyelitis, abscess, or mycotic aneurysm</td>
<td>[36]</td>
</tr>
<tr>
<td><em>Fusobacterium necrophorum</em></td>
<td>Lemiére syndrome (often fatal)</td>
<td>[37]</td>
</tr>
</tbody>
</table>

NOTE. BSI, bloodstream infection; IE, infective endocarditis.
emia, to enable identification of the organism responsible to the species level, and to prompt a more thorough diagnostic workup to identify the source of infection. Otherwise, early antimicrobial treatment of a patient with a presumed BSI or a BSI confirmed by a single positive blood culture result may mask the true diagnosis of the underlying origin of infection.

Blood isolates should always be identified to the species level, even if they initially appear to be contaminants. Full identification of the infecting pathogen may lead to alternative treatment options and may provide clues to the diagnosis and sometimes also the prognosis [21]. For example, *S. anginosus* is typically associated with abscess formation in the brain, lungs, liver, and gastrointestinal tract. Other microorganisms, if isolated from a blood culture, are also often indicative of a specific infectious disease (table 2).

**CASE STUDY 2**

A 64-year-old man had a history of myocardial infarctions in 1976 and 1984. He experienced severe congestive heart failure (left ventricular ejection fraction, 30%) and received a double coronary artery bypass graft in 1997. In 1999, he received a cardiac transplant and was fitted with an implantable cardioverter defibrillator. In 2001, he presented with dyspnea, unproductive cough, and low-grade fever.

Initial diagnostic evaluation using bronchoalveolar lavage revealed normal flora but no pathogenic microorganisms, including fungi and mycobacteria. A chest radiograph revealed a localized opacity in the lower right lung. Lung cancer was suspected on the basis of the morphology of the lesion (figure 4), and lung surgery (i.e., lobectomy) was arranged. After hospital admission, an initial blood culture yielded gram-positive bacteria that were identified as diphtheroids and were considered to represent a common skin contaminant. A second blood culture was recommended and yielded gram-positive bacteria that were then considered to be a true pathogen and were finally identified as *Rhodococcus equi*. This organism is an established agent of pneumonia in immunocompromised hosts and requires a dedicated therapeutic approach. On the basis of these findings, bacterial pneumonia was diagnosed, and surgery was cancelled. Three months of treatment with erythromycin resulted in a complete clinical recovery and resolution of abnormal radiographic findings without the need for removal of any lung tissue (figure 5).

In this case, the symptoms and radiographic findings suggested malignancy, rather than infection. Microbiological findings (i.e., the subsequent isolation and identification of a known, rare respiratory pathogen in the blood) were the key to the diagnosis of an infectious disease caused by an opportunistic pathogen that required antimicrobial treatment instead of surgical intervention.

**CASE STUDY 3**

A 63-year-old man presented to an ophthalmology clinic with blurred vision in October 2006. He had a history of weight...
loss of 10 kg in 8 weeks, prostration, and a subfebrile body temperature of 37.9°C. Blood cultures revealed that the infecting organism was *Streptococcus bovis*, a typical cause of IE. Transesophageal echocardiography was performed and showed a small vegetation on the aortic valve. The patient had a good clinical response to treatment with penicillin G and gentamicin. However, in search of the portal of entry for *S. bovis*, colonoscopy, endorectal ultrasound, and magnetic resonance tomography indicated that the source of infection was colonic carcinoma (figures 6–8).

The identification of *S. bovis* as the infecting organism was consistent with the observed IE. However, the identification of this organism also prompted the ultimate identification of colonic carcinoma, which is an underlying risk factor for *S. bovis* bacteremia. An association between *S. bovis* IE and colorectal carcinoma was reported in case studies in the 1970s [38, 39]. In case-control studies, the relative risk of developing IE from *S. bovis* in the presence of colonic carcinoma was 3%–6%, whereas 60%–75% of patients with IE associated with *S. bovis* infection also have previously undiagnosed malignant gastrointestinal disease [40]. Among patients with *S. bovis* bacteremia, estimates of the percentage with colonic neoplasms have ranged from 6% to 58% [29]. *S. bovis* bacteremia may provide an early indication of serious gastrointestinal disease [41]. Therefore, gastrointestinal tract evaluation should be included for all patients with *S. bovis* bacteremia, regardless of the presence of IE [30, 41].

**CASE STUDY 4**

A 52-year-old man was found unconscious in his home in June 2002. Cerebral CT scan revealed subarachnoid bleeding. After admission to and treatment in a neurological intensive care unit, the patient developed ventilator-associated pneumonia, and culture of a bronchial aspirate specimen yielded *Escherichia coli*. The patient was treated with imipenem for 1 week and recovered from pneumonia. However, a few days later, he developed a spiking fever, and the central venous catheter was removed on day 14 of treatment. Both blood and catheter-tip cultures yielded *E. coli*. Treatment with ciprofloxacin, to which the organism was also susceptible, was initiated, and the fever resolved. Follow-up blood cultures obtained over 3 days while the patient was receiving adequate antimicrobial therapy were still positive for *E. coli*, but transesophageal echocardiography showed no abnormalities indicative of right-sided IE. Further analyses, including contrast-enhanced chest CT, revealed an infected thrombus in the brachiocephalic vein. Intravenous heparin treatment was started, and treatment with ciprofloxacin was continued for a period of 4 weeks; subsequently, the results of blood cultures were negative. There was no recurrence of BSI after treatment was stopped.

This case highlights the importance of always considering the use of follow-up blood cultures to document eradication of the infecting organism, even if no symptoms of recurrence or continuing infection are observed. A positive result of follow-up blood culture while the patient is receiving effective treatment usually indicates a complication and may suggest an intravascular source, such as IE, mycotic aneurysm, or suppurative thrombophlebitis. Follow-up cultures for patients with *S. aureus* BSI are particularly important.

**CONCLUSIONS**

Clinically defined BSIs are always significant. Determining whether these are primary or are associated with an infection at another site is a priority in selecting the most appropriate management strategy and requires a thorough examination, including microbiological, laboratory, and imaging studies. However, early and appropriate empirical therapy that takes into consideration the most likely pathogen may need to be initiated depending on the health status of the patient.
Robust microbiological investigations that include identification of blood isolates to the species level are central to informing and directing efficient and effective diagnostic examinations and to choosing the optimal antimicrobial regimen. In addition, identification of the causative organism may identify other pathologies that would not always have been suspected on clinical grounds. The significance of microbiological findings, in particular a positive result of blood culture, should not be underestimated, even when there is an apparent resolution of symptoms. If the results of microbiological analysis are not consistent with the clinical diagnosis, additional diagnostic tests should be performed until the significance of the microbiological finding is clearly refuted or until the existence of a deep-seated infection is established. Although early and appropriate treatment of infections is a high priority, immediate antimicrobial therapy for a febrile but clinically stable patient with a suspected (but not positively identified) infection might not always be the best option and should be assessed on a case-by-case basis.

The case studies described here highlight the importance of several recommendations for the diagnostic evaluation of BSIs. First, care should be taken not to misdiagnose a BSI without a clinically apparent source as a primary BSI when the bacteremia resolves quickly, spontaneously, or with treatment. A thorough diagnostic examination is always necessary to rule out a primary site of infection that may require a different therapeutic approach—that is, source control in addition to antimicrobial therapy. Multiple blood culture sets may be required to obtain an accurate diagnosis, and it may be necessary to consider delaying the initiation of antimicrobial therapy to enable identification of the causative microorganism. Second, identification of the infecting pathogen to the species level may suggest associations with other pathologies (e.g., the association between S. bovis bacteremia and gastrointestinal neoplasms or between S. anginosus bacteremia and a deep-seated abscess) and may enable identification of previously undiagnosed disease. In instances when such associations may occur, further evaluations should be conducted to determine whether other pathologies are present (e.g., colonoscopy in the case of S. bovis bacteremia) and to permit the identification and treatment of hitherto undiagnosed disease. Third, in all cases, it is important to consider use of follow-up blood cultures to document eradication of the infecting organism, even if there are no obvious symptoms of recurrence or continuing infection.

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