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Bacteremia Can Be a Serious Health Problem

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Abstract

Bacteremia means the penetration of bacteria into the bloodstream. It can occur spontaneously, due to the introduction of urinary or IV catheters or after dental procedures or procedures on the digestive and urogenital system, wound care or other procedures. Bacteremia can cause metastatic infections, including endocarditis, especially in people with heart valve disease. Transient bacteremia is often asymptomatic, but can cause fever. The appearance of other symptoms usually indicates a more severe infection, such as sepsis or septic shock. Patients with certain heart diseases should receive antibiotic prophylaxis before the procedure, which can cause significant bacteremia. Bacteremia may be transient and cause no consequence, or it may cause metastatic and systemic consequence.

Keywords: Bacteremia, FUO, Infection, Sepsis, Septic Shock, Health

Introduction

Bacteremia, the presence of bacteria in the bloodstream, was recognized more than a century ago [1]. Bacteremia accounts for approximately 5–15% of all health care–associated infections and remains a major cause of morbidity and mortality. Case fatality rates are high ranging from 10% to 60%. In addition to being an important cause of death, bloodstream infections lead to prolonged length of hospitalizations and higher cost of care. Bacteremia is classified as community-acquired, health care–associated, and hospital-acquired. Bacteremia can be further classified as primary or secondary. Primary bacteremia is a documented bloodstream infection without a known source. In the presence of an indwelling catheter, a primary bacteremia is considered a catheter-related bloodstream infection. These device-related nosocomial bloodstream infections have increased eightfold over the past decades.

Bacteremia refers to the presence of viable bacteria in blood [2]. To gain access to the circulation, bacteria and their toxins must penetrate through protective mechanisms such as anatomic barriers (skin), the nonspecific immune system, and the specific immune system. Bacteremia can range from a benign asymptomatic course to a more continual infection that can progress to septic shock or TSS (toxic shock syndrome). Bacteremia can be described as primary (direct invasion of blood stream, as in intravenous [IV] drug use) or secondary (infection at another site complicated by microorganisms invading the bloodstream, as in pneumonia or soft-tissue infections). It can present as:

- Transient Bacteremia – short periods (minutes to hours) of viable bacteria in blood usually with normal flora pathogens. Common during toothbrushing, routine dental work, and menstruation. It is usually cleared by the reticuloendothelial system.
- Intermittent Bacteremia – recurrent episodes of viable bacteria from extravascular abscesses, spreading cellulitis, or body infections such as septic arthritis, peritonitis, or an empyema.
- Continuous Bacteremia – usually occurring when infection is intravascular, such as with infected endothelium seen in infective endocarditis or with infected hardware as with an indwelling catheter.

FUO

The primary considerations in diagnosing nosocomial FUO (Fever of unknown origin) are the underlying susceptibility of the patient coupled with the potential complications of hospitalization [3]. The original surgical or procedural field is the place to begin a directed physical and laboratory examination for abscesses, hematomas, or infected foreign bodies. More than 50% of patients with nosocomial FUOare infected, and intravascular lines, septic phlebitis, and prostheses are all suspect. In this setting, the approach is to focus on sites where occult infections may be sequestered, such as the sinuses of intubated patients or a prostatic abscess in a man with a urinary catheter. Clostridium difficile colitis may be associated with fever and leukocytosis before the onset of diarrhea. In 25% of patients with nosocomial FUO, the fever has a noninfectious cause. Among these causes are acalculous cholecystitis, deep-vein thrombophlebitis, and pulmonary embolism. Drug fever, transfusion reactions, alcohol/drug withdrawal, adrenal insufficiency, thyroiditis, pancreatitis, gout, and pseudogout are among the many possible causes to consider. As in classic FUO, repeated meticulous physical examinations, coupled with focused diagnostic techniques, are imperative. Multiple blood, wound, and fluid cultures are mandatory. The pace of diagnostic tests is accelerated, and the threshold

for procedures—CT scans, ultrasonography, In-WBC scans, noninvasive venous studies—is low. Even so, 20% of cases of nosocomial FUO may go undiagnosed.

Like diagnostic measures, therapeutic maneuvers must be swift and decisive, as many patients are already critically ill. Intravenous lines must be changed (and cultured), drugs stopped for 72 h, and empirical therapy started if bacteremia is a threat. In many hospital settings, empirical antibiotic coverage for nosocomial FUO now includes vancomycin for coverage of methicillin-resistant Staphylococcus aureus as well as broad-spectrum gram-negative coverage with piperacillin/ tazobactam, ticarcillin/ clavulanate, imipenem, or meropenem. Practice guidelines covering many of these issues have been published jointly by the Infectious Diseases Society of America (IDSA) and the Society for Critical Care Medicine and can be accessed on the IDSA website.

Infections

Bloodstream infections are a common and serious problem with a high mortality rate [1]. Numerous studies have demonstrated that a delay in empiric antibiotic treatment is associated with an increase in this already high mortality rate. In turn, the initiation of appropriate and effective treatment is dependent on an accurate diagnosis established in a timely fashion. More rapid diagnosis of bacteremia allows for a more expeditious implementation of appropriate antimicrobial treatment and reduces morbidity and mortality.

Blood cultures are the current cornerstone for detection of bloodstream infections. A blood culture is defined as a specimen of blood obtained from a single venipuncture or intravascular access device. Over the past 30 years,numerous changes have been made to blood culture media and systems with the goal of improving sensitivity and speed of diagnosis.

Septic Shock

The clinical presentation of shock varies with the type and cause, but several features are common including hypotension (defined as systolic blood pressure less than 90 mmHg), cool clammy skin and oliguria (due to redistribution of blood), changes in mental status (confusion, delirium, or coma), and metabolic acidosis [4]. Sepsis refers to a clinical syndrome that encompasses a variety of host responses to systemic infection. As discussed above, the clinical spectrum of sepsis depends primarily on the host response to infection rather than the severity of the infection itself. Because the clinical manifestations of sepsis can be recapitulated experimentally by infusing proinflammatory mediators (such as interleukins and TNF – α (tumor necrosis factor)), an exaggerated host inflammatory response is felt to be central to its pathophysiology. Although various risk factors have been identified and scoring systems developed, there is as yet no effective method to predict which patients will progress from bacteremia to septic shock and MODS (multiple - organ system dysfunction syndrome). In general, however, more severe inflammatory responses appear to be accompanied by progressively greater mortality rates. The timing of onset of infection may also infl uence the clinical outcomes. A recent study showed that patients who developed septic shock within 24 hours of ICU (intensive care unit) admission were more severely ill but had better outcomes than patients who became hypotensive later during their ICU stay.

The clinical manifestations of septic shock fall into three broad categories, which correlate with progressive physiologic derangement. Early (warm) shock is characterized by a hyperdynamic circulation and decreased SVR (systemic vascular resistance). The hallmark of late (cold) shock is abnormal tissue perfusion and oxygenation due to regional (peripheral) vasoconstriction and myocardial dysfunction. Secondary (irreversible) shock is frequently a terminal condition associated with multiple - organ system dysfunction. Each phase represents a continued downward progression in the course of this disease process.

In the early phase of septic shock, bacteremia is heralded typically by shaking chills, a sudden rise in temperature, tachycardia, and warm extremities. Although the patient may appear ill, the diagnosis of septic shock may be elusive until hypotension is evident. In addition, patients may present initially with non - specific complaints such as malaise, nausea, vomiting, or even profuse diarrhea. Abrupt alterations in behavior and mental status changes, which have been attributed to a reduction in cerebral blood flow, may also herald the onset of septic shock. Tachypnea or dyspnea may be present with no objective findings on physical examination. These symptoms likely represent a direct effect of endotoxin on the respiratory center and may precede the development of clinical ARDS (Acute Respiratory Distress Syndrome).

Sepsis

Sepsis is defined as infection-provoked systemic inflammatory response syndrome (SIRS) [5]. If acute organ dysfunction or hypotension accompanies SIRS, severe sepsis is present. Septic shock is severe sepsis accompanied by refractory hypotension. Primary sepsis is the sepsis syndrome or septic shock in the absence of a clear source of infection. Secondary sepsis is the development of hemodynamic instability and recurrent sepsis syndrome despite adequate antimicrobial therapy for a known initial source of infection. Primary and secondary sepsis may be bacterial or nonbacterial in nature. In addition, a number of noninfectious syndromes can mimic the clinical picture observed in sepsis.

If mental obtundation or nuchal rigidity is present or there is concern for central nervous system (CNS) pathology, head computed tomography (CT) and lumbar puncture should be performed to evaluate for meningitis. If productive cough, shortness of breath, or other respiratory symptoms are present, sputum should be sent for Gram's stain, culture, and susceptibility. Thoracentesis should be performed to rule out an empyema if there is a pleural effusion. If purulent nasal drainage is present, CT of the sinuses should be performed with a plan to aspirate the sinuses if there is an air-fluid level. If indwelling vascular devices are present, one set of blood cultures should be drawn through the device. If the site looks infected or in the setting of bacteremia, the catheter should be removed and sent for culture. Also, transesophageal echocardiography should be considered to evaluate for endocarditis. If ascites or indwelling drains are present, the peritoneal or drain fluid should be sampled and sent for Gram's stain and culture. Also, abdominal imaging with CT or ultrasound should be considered. If there is a history of nephrolithiasis, pyelonephritis, or other renal pathology, renal ultrasound should be ordered to assess for a perinephric abscess and to exclude urinary obstruction. If swollen, hot, tender joints are present, septic arthritis should be ruled out with aspiration of the affected joint. If persistent bacteremia and focal bony pain are identified, plain films or bone scan should be ordered to evaluate for osteomyelitis.

Identification of the source of sepsis is imperative [6]. If the offending tissue bed is not drained or if bacteremia is not treated, outcome will be adversely affected. Evaluation of the patient's history is essential to determine likely sources. Once the probable origin has been identified, appropriate antimicrobial therapy can be instituted to provide coverage for organisms commonly encountered. When a likely source cannot be identified, empirical broad-spectrum therapy should be instituted with drugs known to be effective against gram-positive, gramnegative, and anaerobic organisms. In surgical patients who have had abdominal procedures, enteric gram-negative and anaerobic organisms are of particular concern. Attention must be given to dosing in these patients because alterations in renal function may affect degradation and because an expanded plasma volume affects the volume of distribution and therefore the size of the loading dose that must be given.

Catheter Care

Catheter care is required to prevent malfunction and infection [7]. Malfunction is usually related to thrombus or fibrin-sheath formation. Pre-

vention with any particular type of locking solution is not proven. Most institutions continue to use heparin or 4% citrate as dictated by local policy. When catheter dysfunction is present, line reversal may be successful and is associated with acceptable recirculation.

Infection is prevented by use of excellent local care. Infection rates in acute catheters are minimized with the use of local antibiotic ointment with a dry gauze at the exit site. Bacteremia is associated with the development of an exit-site infection and the duration of catheter use. For femoral catheters the risk of infection rises dramatically after 1 week, and the risk of internal jugular catheter-associated bacteremia rises after 3 weeks: it is reasonable to try to limit catheter duration to within these periods. Once catheter exit-site infection is recognized, the catheter should be removed as the risk of bacteremia rises within days, even when treated – by 2% at 24 hours and 13% at 48 hours. Catheter-associated bacteremia is treated with catheter removal and intravenous antibiotics.

Bacterial Infections in Children

Infants aged 29–60 days are at risk of developing a variety of invasive bacterial infections [8]. Febrile infants without a focus of infection can be divided into those who appear toxic versus nontoxic, and those at low risk versus higher risk of invasive bacterial disease. As with febrile neonates, toxic children in this age group should be admitted to the hospital for parenteral antibiotics and close observation. Viral illness is the most common cause of fever in this age group; if there is evidence of viral disease (upper respiratory infection, bronchiolitis), further workup may not be necessary. Urinary tract infection is the most common bacterial cause of infection in this age group. Nontoxic low-risk infants in this age group are typically treated as outpatients with close follow-up.

In an era of increasing immunization coverage against the most common invasive pneumococcal serotypes, it is difficult to estimate the risk of occult bacteremia in febrile 3- to 36-month-olds with no focus of infection. Nevertheless, when assessing children aged 3–36 months with temperatures of 39°C or higher, urine cultures should be considered in all male children younger than 6 months and in all females younger than 2 years. Chest radiographs should be performed in any child with increased work of breathing and should also be considered in children with high (20,000/mm3) WBC (white blood cells) counts but no respiratory symptoms. Depending on the child's appearance, underlying medical condition, and height of fever, blood cultures should also be obtained. Empiric antibiotic therapy may be considered, particularly for children with temperature of 39°C and WBC count of 15,000/mm3. However, in previously healthy, wellappearing, fully immunized children with reassuring laboratory studies, observation without antibiotics is appropriate.

Bacteremia is defined as the recovery of bacteria in a blood culture [9]. This may be a transient phenomenon not associated with any significant disease (e.g., after instrumentation of the gastrointestinal or genitourinary tract) or may result from extension of an undiagnosed invasive bacterial infection elsewhere. When a positive bacterial blood culture is obtained from an otherwise healthy-appearing child without a known source of infection, it is termed occult bacteremia. If the child's immune system is unable to effectively eliminate the bacteria, a systemic inflammatory response may occur. Sepsis is the term used to describe this systemic inflammatory response. If sepsis is not recognized and treated early, it may progress to overwhelming infection, septic shock (i.e., sepsis with hypotension), multiple organ dysfunction syndrome, and death. Severe sepsis is a more advanced sepsis that has progressed to cause failure in multiple organ systems (e.g., brain, kidneys, heart). Septic shock may be recognized by a clinical triad of hyperthermia or hypothermia, altered mental status, and flash capillary refill and bounding pulses (warm shock) or mottled cool extremities and diminished pulses (cold shock). Of note, hypotension is a late finding of septic shock and is not necessary to make the diagnosis. Meningitis is an extension of infection to involve the meninges of the CNS.

Testing

The gold standard for diagnosing bacteremia remains the traditional microbiology laboratory broth blood culture followed by identification and susceptibility testing [10]. Novel molecular techniques that use genetic analysis for molecular organism detection including hybridization (fluorescence in situ hybridization [FISH], arrays), amplification (polymerase chain reaction [PCR], multiplex PCR), post-amplification detection (PCR 1 hybridization/MALDI-TOF mass spectrometry [MS]), and non-nucleic acid-based strategies (proteomics, spectrometry) are rapidly gaining ground. PCR and multiplex post-amplification techniques accelerate the diagnosis of bacteremia and detection of the most common resistant genotypes. However, the majority of molecular tests require a positive blood culture before widespread clinical application. The main benefits of pathogen detection by PCR, multiplex PCR, and MS is the possibility of having results reported as soon as 6 hours after sampling. To our knowledge, there has been no large, multicenter, multinational randomized controlled trial (RCT) comparing conventional blood culture to a strategy of blood culture plus molecular organism detection in sepsis.

Barriers to the universal approval of PCR detection of pathogens include limited sensitivity of the test (i.e., statistical sensitivity), discordance between molecular results and blood cultures (i.e., specificity), and a poor ability to detect Streptococcus pneumoniae bacteremia (i.e., sensitivity). Several molecular strategies allow molecular detection of pathogens: pathogen-specific assays targeting species- or genusspecific genes; assays targeting conserved sequences in the bacterial or fungal genome (panbacterial 16S, 5S, or 23S rRNA genes or panfungal 18S, 5.8S, and 28S rDNAs), and multiplex assays allowing parallel detection of different pathogens.

The most used molecular pathogen detection test is the SeptiFast test (Roche Diagnostics), a multiplex real-time PCR-based assay that detects 25 pathogens with modest sensitivity for detection of bacteremia. However, SeptiFast had variable pathogen detection compared with traditional blood culture testing. In a prospective severe sepsis study, PCR positivity even with a negative blood culture was associated with higher sequential organ failure assessment (SOFA) scores and a trend towards higher mortality.

Treatment

Successful management of bacteremia requires elimination of the offending pathogen by the timely administration of antibiotics and removal of the source of infection [2]. Bacteremia should be treated if one obtains 2–4 positive blood cultures; sensitivity is dependent on the volume of blood cultured, with 30–40 mL per session being recommended for optimal results. One must draw at least 10 mL of blood for culture by venipuncture with at least 10 mL through each lumen of a central vascular catheter when one is present. Empiric antimicrobial therapy of bacteremia and sepsis depends upon localizing the site of infection to a particular organ, which determines the pathogenic flora in the septic process. The usual pathogens are determined by the organ or infection site, are predictable, and are the basis for the selection of appropriate empiric antimicrobial therapy. Coverage should be directed against the most common pathogens and does not need to be excessively broad or contain unnecessary activity against uncommon pathogens. If multiple drugs are used initially, the regimen should be modified and coverage narrowed based on the results of culture and sensitivity testing.

For TSS, hemodynamic stabilization and antimicrobial therapy are the initial goals of treatment. Immediate and aggressive management of hypovolemic shock is critical. Thus, fluid resuscitation with crystalloid or colloidal solution is important in the mainstay of treatment. Tampons or other packing material should be promptly removed. It is often difficult to

determine initially whether Streptococcus or Staphylococcus is the offending bacterium, so coverage for both is necessary. Suggested regimens include penicillin plus clindamycin, erythromycin, or ceftriaxone plus clindamycin. Patients with suspected methicillinresistant staphylococcal TSS should be treated with IV vancomycin 1 g every 12 hours for 10–15 days, with dose adjustment based on creatinine clearance. Patients with streptococcal TSS require hospitalization for care, usually initially in an intensive care setting. Patients with streptococcal TSS should be treated with both IV penicillin G, 3–4 million units every 4 hours, and IV clindamycin, 600–900 mg every 8 hours for 10–15 days, followed by oral therapy. Double antibiotic coverage is the standard of care for streptococcal TSS because this infection is characterized by extremely large numbers of stationary bacteria and penicillin alone is not effective in this scenario.

Conclusion

Bacteremia indicates the presence of bacteria in the bloodstream. Sepsis is more likely when there is an infection in the body, such as in the lungs, abdomen, urinary system or skin. Sepsis can also occur when surgery is performed on an infected area or part of the body where bacteria normally grow, such as the intestines. Placing any foreign body - such as an intravenous catheter, urinary catheter or drain - can also cause sepsis. The longer the object is in place, the more likely it is to develop sepsis. The development of symptoms such as tachypnea, tremor, persistent fever, altered sensations, hypotension, and digestive symptoms (abdominal pain, nausea, vomiting, and diarrhea) indicate sepsis or septic shock. Septic shock develops in 25 to 40% of patients with significant bacteremia.

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