Management Of Fever And Suspected Infection In Pediatric Patients With Central Venous Catheters

Abstract

The use of indwelling central venous catheters is essential for pediatric patients who require hemodialysis, parenteral nutrition, chemotherapy, or other medications. Fever is a common chief complaint in the emergency department, and fever in a patient with a central venous catheter may be related to a common cause of fever, or it may be due to a catheter-associated bloodstream infection. Catheter-associated bloodstream infections may also lead to additional complications such as sepsis, septic shock, or septic complications including supplicative thrombophlebitis, endocarditis, osteomyelitis, septic emboli, and abscesses. Early resuscitation as well as timely and appropriate antibiotic therapy have been shown to improve outcomes. This issue focuses on the approach to fever in pediatric patients with central venous catheters and the management and disposition of patients with possible catheter-associated bloodstream infections.

December 2015
Volume 12, Number 12

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CME Objectives
Upon completion of this article, you should be able to:
1. Describe the presentation of infections related to central venous catheters.
2. Identify common organisms known to cause catheter-associated bloodstream infections in different patient populations.
3. Determine appropriate initial empiric antibiotic therapy for patients with central venous catheters presenting with fever.
4. Recognize the signs and symptoms of sepsis in patients with a central venous catheter who present with fever and provide appropriate and timely therapies.

Prior to beginning this activity, see “Physician CME Information” on the back page.

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Case Presentations

An 8-year-old boy with a history of standard-risk acute lymphoblastic leukemia presents to the ED with a fever. He has a port central line and is currently undergoing the delayed intensification phase of chemotherapy. He last received chemotherapy 1 day prior to presentation. He also reports a headache and a cough. Upon examination, he is febrile to 39.2°C, with a heart rate of 120 beats/min and blood pressure of 108/60 mm Hg. He is breathing comfortably and has an oxygen saturation of 99% on room air. You consider what initial laboratory workup you might need…

A 4-year-old girl with a history of gastroschisis requiring intestinal resection that resulted in short gut syndrome presents with a history of fever, vomiting, and diarrhea. She is dependent upon total parenteral nutrition, which is delivered through a Broviac® catheter. She has a history of multiple previous line infections, including a recent MRSA line infection. On examination, her temperature is 38.2°C, and she has a heart rate of 105 beats/min and blood pressure of 100/55 mm Hg. You wonder what initial laboratory testing and imaging you should consider, and what the appropriate disposition for this patient should be…

Introduction

Fever is a common chief complaint of pediatric patients presenting to the emergency department (ED), and patients with a central venous catheter (CVC) may also have common causes of fever similar to children without pre-existing medical conditions. While these common causes of fever may occur in patients with CVCs, it is imperative that emergency clinicians investigate all episodes of fever for catheter-associated bloodstream infections (CA-BSI), and initiate prompt and appropriate antibiotic therapy if catheter-associated infection is suspected.

The use of an indwelling CVC is essential in pediatric patients who require hemodialysis, parenteral nutrition, frequent blood draws, frequent blood product transfusions, or long-term intravenous medications (such as antibiotics or chemotherapeutics). Although essential to the treatment of these patients, there are several complications that may arise with the ongoing use of CVCs. In addition to catheter dysfunction, thrombosis, and embolization, patients with a CVC may also experience infection at the insertion site, the tunneled portion of the catheter, the subcutaneous pocket of a totally implanted intravascular device (a pocket infection), or within the catheter itself. The indwelling catheter provides a portal of entry for bacteria (and other organisms), and renders these patients susceptible to the development of a CA-BSI and the potential for progression to overwhelming infection and sepsis.

The rapid recognition and triage of these patients, with subsequent initiation of antibiotics and resuscitative measures, has been studied extensively and has been shown to improve outcomes in febrile neutropenic patients with indwelling central catheters.1 The time to antibiotic therapy has been consistently used as a quality-of-care measure in this patient population.2 Although less-studied in other pediatric populations relying on CVCs, a regular complication in these patients remains the occurrence of CA-BSI. Sepsis syndrome remains a leading cause of morbidity and mortality in pediatric patients, and the Surviving Sepsis Campaign (www.survivingsepsis.org) recommends initiation of empiric antibiotic therapy within 1 hour of the recognition of severe sepsis or septic shock in both adult and pediatric patients.

Critical Appraisal Of The Literature

An online search for literature from 1980 to the present was performed using the Pubmed and MEDLINE® databases. Search terms included fever, central venous catheter, and infection. More than 6000 articles were found using the search terms and included case reports, review articles, and prospective and retrospective studies. This was narrowed by limiting the results to studies involving children aged 0 to 18 years, and articles published in English. A search on Ovid® produced 662 articles, which were analyzed and further refined to 73 relevant articles. Two clinical practice guidelines were also included in the results. A search of the Cochrane Database of Systematic Reviews was also conducted. There is a significant amount of literature on fever or infection with a CVC in the pediatric hematology-oncology population; however, there is a relative paucity of literature specific to other patient populations, such as pediatric patients on dialysis, patients with intestinal failure, patients dependent upon parenteral nutrition, and other subsets commonly requiring long-term central venous access. Very little information is available on the evaluation and acute management of fever in patients with a CVC in the ED.

Etiology And Pathophysiology

There are several different types of indwelling CVCs used in pediatric patients who have a need for long-term vascular access. These catheters are either peripherally inserted central catheters (PICCs), surgically placed central catheters, or totally implanted devices or ports. Surgically placed catheters include tunneled or nontunneled partially implanted catheters. (See Table 1, page 3.) The choice of catheter used in each patient is based upon the length of time that the catheter is needed, the reason for its use, and patient-related factors such as age, size, or patient and family preferences. Complications of the long-term use of all types of catheters include mal-
function, line fracture or leakage, and thrombosis, as well as infectious complications such as tunnel or pocket infections, CA-BSI, metastatic infections, and sepsis.3,4,5

The terms catheter-related bloodstream infection (CR-BSI) and CA-BSI are often used interchangeably by clinicians. However, they differ in the degree of proof of infection that is required for the diagnosis.

**Catheter-Related Bloodstream Infection**

CR-BSI is a term used for research purposes, and is defined by a positive peripheral culture and either a positive culture from the catheter tip or differences in the time between the growth between catheter and peripheral culture specimens. Additionally, 1 of the following must also be present: (1) a positive semiquantitative culture (> 15 colony-forming units/catheter segment); (2) a positive quantitative blood culture (> 103 colony-forming units/catheter segment) of the same organism; (3) paired peripheral and catheter quantitative blood cultures that have a ratio of > 3:1 colony-forming units/mL of blood (catheter vs peripheral); or (4) a differential time to positivity of growth of an organism from the sample drawn from the catheter hub that is at least 2 hours before growth detected from the peripheral vein.6-9

**Catheter-Associated Bloodstream Infection**

A CA-BSI is a primary bloodstream infection (any laboratory-confirmed bloodstream infection not related to another source) or clinical sepsis in the presence of an intravascular device.10,11 In pediatric patients, a diagnosis of CA-BSI is more likely since peripheral blood cultures are not often obtained. Since a confirmed diagnosis requires time for cultures to grow, it must be assumed that the catheter is the source of fever in these patients in order to provide timely treatment.

CA-BSIs remain a significant cause of morbidity and mortality in pediatric patients. The incidence of CA-BSIs varies and is based on several catheter- and patient-related factors. Catheter-related factors include the catheter type, the number of catheter lumens, the location of insertion, and the duration of catheter placement.13 Factors associated with early infection after placement of a CVC include the presence of neutropenia at the time of CVC insertion and failure to provide perioperative antibiotics at the time of insertion.14

**Table 1. Types Of Central Venous Catheters**6,10-12

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary central catheters</td>
<td>• Rapid bedside placement</td>
</tr>
<tr>
<td></td>
<td>• Can have single or multiple lumens</td>
</tr>
<tr>
<td></td>
<td>• Intended for short-term use in inpatient setting only</td>
</tr>
<tr>
<td></td>
<td>• Highest infection risk</td>
</tr>
<tr>
<td>Peripherally inserted central catheters</td>
<td>• Used for short- or long-term access</td>
</tr>
<tr>
<td></td>
<td>• Can be placed at bedside</td>
</tr>
<tr>
<td></td>
<td>• Introduced into a peripheral vein and threaded to terminate in a central</td>
</tr>
<tr>
<td></td>
<td>location</td>
</tr>
<tr>
<td>Long-term tunneled central venous</td>
<td>• Surgically placed, tunneled portion under skin with lumen exiting from skin</td>
</tr>
<tr>
<td>catheters (Broviac®, Hickman®,</td>
<td>• Catheter has a cuff that sits under the skin and helps keep the catheter</td>
</tr>
<tr>
<td>Groschong®, NeoStar™)</td>
<td>in place</td>
</tr>
<tr>
<td></td>
<td>• Can have single lumen or multiple lumens</td>
</tr>
<tr>
<td>Totally implanted ports</td>
<td>• Surgically placed</td>
</tr>
<tr>
<td></td>
<td>• Entirely buried under the skin</td>
</tr>
<tr>
<td></td>
<td>• Can only be accessed by a specific Huber needle</td>
</tr>
<tr>
<td></td>
<td>• Lowest infection risk</td>
</tr>
</tbody>
</table>

**Association Of Catheter Type And Infectious Complications**

Several studies have examined the association of catheter type and rate of infectious complications. Of the various catheters used for central access, totally implanted catheters (ports) are associated with the lowest risk of infection. A study examining both CVC- and patient-related factors influencing the risk of infectious complications in pediatric patients receiving chemotherapy demonstrated that the type of CVC was significantly associated with the incidence of bloodstream infection with a hazard ratio (the chance of a bloodstream infection occurring) for tunneled externalized catheters and peripherally inserted central catheters of 2.16 and 1.43, respectively, when compared to totally implanted devices.15 Another study by Newman et al compared infection rates between Hickman® catheters and implanted ports in pediatric cancer patients. Of the 178 CA-BSIs in 93 patients, more infections were recorded among patients with Hickman® catheters than ports.16 Similar results were found in the study by Adler et al that compared infection rates between Hickman® catheters and implanted ports. The study showed that infectious complications were more frequent in the Hickman® catheter group, and that the time from catheter insertion to the first catheter-associated infection was shorter in patients with Hickman® catheters than with ports.17 In another retrospective cohort study, the risk of bacteremia in patients with external catheters (such as Hickman® or Broviac® catheters) was 4 times that of implanted catheters.18

Of the surgically placed partially implanted devices such as Hickman® or Broviac® catheters, there is evidence that catheters with multiple lumens are associated with the highest infection risk. In an observational study comparing complication rates
between double- and single-lumen Hickman® and Broviac® catheters, as well as pressure-activated safety valve catheters inserted in pediatric oncology patients, double-lumen catheters had the highest rate of reported infectious complications among all catheters, with 56 out of 114 complications.\(^7\)

**Other Factors Affecting Infection Rate**
In addition to catheter-related factors, a number of additional factors have been noted to increase the infection rate. These include younger age of the patient (< 3 years), use of the catheter for parenteral nutrition or chemotherapy, lower body weight (< 8 kg), or the presence of neutropenia or patients who have undergone stem cell transplantation.\(^{19-26}\)

**Infectious Pathogens**
According to the 2009 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infections, the most common pathogens causing CA-BSI from surgically implanted catheters and peripherally inserted CVCs in both children and adults are coagulase-negative staphylococci, Staphylococcus aureus, enteric gram-negative bacilli, and Pseudomonas aeruginosa. In the pediatric population, S aureus and coagulase-negative staphylococci were found to be the most common pathogens overall.\(^6\)

**Table 2. Common Organisms Causing Infection In Patients With Central Venous Catheters\(^6,20,27-34\)**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Common Micro-organisms</th>
</tr>
</thead>
</table>
| Patients with surgically implanted or peripherally inserted central venous catheters | • Coagulase-negative staphylococci\(^*\)  
• Staphylococcus aureus\(^*\)  
• Enteric gram-negative bacilli  
• Pseudomonas aeruginosa |
| Intestinal failure/parenteral nutrition-dependent patients | • Escherichia coli  
• Coagulase-negative staphylococci  
• Klebsiella pneumoniae  
• Enterococcus  
• Polymicrobial infections |
| Hemodialysis patients                                   | • Staphylococcus aureus  
• Coagulase-negative staphylococci  
• Enterococci  
• Gram-negative bacteria  
• Mycobacteria  
• Candida species |
| Oncology patients                                       | • Gram-positive organisms  
\(\text{(Staphylococcus epidermidis, coagulase-negative staphylococci, Staphylococcus aureus)}\)  
• Pseudomonas aeruginosa |

\(^*\)Most common in pediatric patients

Specific patient populations must also be considered when thinking about common pathogens causing infection. (See Table 2.) When considering patients who require central venous access for prolonged nutritional therapy, particularly due to intestinal failure, gram-negative enteric organisms are more common cause of infection. Common pathogens detected in this population with varying frequency include *Escherichia coli*, coagulase-negative staphylococci, *Klebsiella pneumoniae*, and *Enterococcus* species.\(^{27-30}\) Although all pediatric patients with indwelling CVCs are at increased risk for polymicrobial infections, patients with underlying gastrointestinal pathology and patients who are dependent upon parenteral nutrition appear to have the greatest risk.\(^{31,32}\) In a review of studies looking at CA-BSI in pediatric hemodialysis patients, the most common pathogens are *S. aureus*, coagulase-negative staphylococci, enterococci, gram-negative bacteria, mycobacteria, and *Candida* species.\(^{33,34}\) In pediatric oncology patients, gram-positive organisms (specifically *Staphylococcus epidermidis*, coagulase-negative staphylococci, and *S. aureus*) are most common, and account for up to 70% of proven bloodstream infections. However, gram-negative organisms continue to play a role in disease in this population with *P. aeruginosa* an important pathogen to consider in neutropenic oncology patients.\(^20\) Children who have a history of multiple CA-BSIs or a history of prolonged antimicrobial therapy are at increased risk for antimicrobial-resistant organisms.

**Pathogenesis**
The pathogenesis of CVC-related infection is complex. In order for a micro-organism to cause infection, it must gain access to the extraluminal or intraluminal surface of the catheter. Extraluminal contamination is often due to common skin pathogens that migrate from the skin to the subcutaneous tract. They are often introduced during placement or manipulation of the catheter, and this method of contamination is the typical cause of catheter-related infection in the first month after catheter placement.\(^35\) Intraluminal contamination can occur when there is colonization of the catheter hub, particularly by common skin organisms. The catheter hub is a usual source of infection in long-term catheters and in tunneled catheters, in particular. The failure to use aseptic techniques during catheter placement or when accessing the catheter is associated with a higher risk of infection.\(^34,35\) More rarely, seeding of the catheter from a distant source of infection or from a contaminated infusate may cause catheter contamination.\(^36\)

Once a micro-organism gains access to the catheter, it can cause local infections, such as exit site infections, tunnel infections, or pocket infections. However, once released into the bloodstream, this pathogen invasion activates a cascade of events that
can cause a wide range of symptoms including fever, tachycardia, tachypnea, vasodilation, and, in the most severe cases, circulatory collapse, end-organ damage, and death.\textsuperscript{37}

**Differential Diagnosis**

Children presenting to the ED with fever and a CVC must be evaluated for a catheter-related source of infection. Catheter-associated infections may be local or systemic.

**Local Infections**

Local infections at the catheter site include phlebitis, exit site infections, tunnel infections, and pocket infections. Common presenting signs include induration, erythema, tenderness, fluctuance, and purulent drainage at the catheter site. Fever is often an associated symptom in local catheter site infections; however, it is not always present.

Phlebitis presents as erythema, induration, and/or tenderness along the tract of a catheterized vein. Exit site infections present with erythema, induration, and/or tenderness within 2 cm of the catheter exit site, and may be associated with fever or purulent drainage from the exit site. A tunnel infection also presents with tenderness, erythema, and/or induration that is > 2 cm from the catheter exit site along the subcutaneous tract of a tunneled catheter (such as a Hickman\textsuperscript{®} or Broviac\textsuperscript{®} catheter). Pocket infections contain infected fluid in a subcutaneous pocket of a totally implanted intravascular device. These infections typically present with tenderness, erythema, and induration over the pocket, and the pockets can often rupture and drain.\textsuperscript{5,38}

**Systemic Infections**

In many cases of a CA-BSI, fever may be the only presenting symptom. However, in addition to fever, some patients with presumed CA-BSI also present with changes in vital signs or laboratory values, meeting the criteria for sepsis. In the pediatric population, sepsis can be defined as a proven or suspected infection in the presence of systemic inflammatory response syndrome (SIRS). Pediatric SIRS criteria include at least 2 of the following: (1) temperature > 38.5°C or < 36°C; (2) changes in heart rate manifested as tachycardia > 2 standard deviations above normal for patient age or bradycardia in patients aged < 1 year; (3) tachypnea with respiratory rate > 2 standard deviations above normal for patient age; and (4) leukocyte count elevated or depressed for age or the presence of > 10% immature neutrophils. (See Table 3.)

The progression to severe sepsis is defined as sepsis with evidence of cardiovascular organ dysfunction, acute respiratory distress syndrome, or evidence of organ dysfunction of ≥ 2 systems. Septic shock is sepsis with evidence of cardiovascular dysfunction (usually hypotension), unexplained acidosis, elevated serum lactate, core-to-peripheral temperature gap > 3°C, prolonged capillary refill time, or oliguria.\textsuperscript{39} Complications of sepsis can also

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Characteristics</th>
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</table>
| Catheter-related bloodstream infection        | Bacteremia or fungemia in a patient who has an intravascular device, > 1 positive blood culture result obtained from the peripheral vein, and no apparent source for bloodstream infection other than the catheter itself, with at least 1 of the following:  
  • A positive semiquantitative culture (> 15 colony-forming units/catheter segment)  
  • A positive quantitative blood culture (> 103 colony-forming units/catheter segment) of the same organism  
  • Paired peripheral and catheter quantitative blood cultures that have a ratio of > 3:1 colony-forming units/mL of blood (catheter vs peripheral)  
  • A differential time to positive growth of an organism from the sample drawn from the catheter hub that is at least 2 hours before growth detected from the peripheral vein |
| Sepsis                                        | • SIRS in the setting of proven or suspected infection  
  • SIRS criteria (must have 2 of 4 criteria, and 1 must be abnormal temperature or leukocyte count):  
    ◦ Core temperature > 38.5°C or < 36°C  
    ◦ Tachycardia (mean HR > 2 standard deviations above normal for age in absence of another explanation) or bradycardia (mean HR < 10th percentile for age) in children aged < 1 year  
    ◦ Mean respiratory rate > 2 standard deviations above mean for age or need for mechanical ventilation  
    ◦ Leukocyte count elevated or depressed for age (not chemotherapy-induced) or presence of > 10% immature neutrophils |
| Severe sepsis                                 | Sepsis plus 1 of the following:  
  • Cardiovascular organ dysfunction  
  • Acute respiratory distress syndrome  
  • Dysfunction of ≥ 2 organs |
| Septic shock                                  | Sepsis and evidence of cardiovascular organ dysfunction (ie, unexplained acidosis, elevated serum lactate, core-to-peripheral temperature gap > 3°C, prolonged capillary refill time, or oliguria) |

Abbreviations: HR, heart rate; SIRS, systemic inflammatory response syndrome.
arise in patients with CA-BSI and include suppurative thrombophlebitis, endocarditis, septic thromboemboli, osteomyelitis, and abscesses.

While there are several infectious complications related to the presence of a catheter, many patients with a CVC presenting with fever will not have a catheter-related infection, and the information obtained on history and physical examination will guide the differential diagnosis. (See Table 4.)

### Table 4. Differential Diagnosis For Fever In Patients With A Central Venous Catheter

<table>
<thead>
<tr>
<th>Local Catheter-Related Causes</th>
<th>Systemic Catheter-Related Causes</th>
<th>Other Causes of Fever Not Associated With the Central Venous Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlebitis</td>
<td>Catheter-related bloodstream infection</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Exit site infection</td>
<td>Sepsis</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Tunnel infection</td>
<td>Severe sepsis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>Septic shock</td>
<td>Acute otitis media</td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td></td>
<td>Abcess</td>
<td>Tonsillitis</td>
</tr>
<tr>
<td></td>
<td>Septic thromboembolism</td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
<td>Conjunctivitis</td>
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<tr>
<td></td>
<td></td>
<td>Lymphadenitis</td>
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<tr>
<td></td>
<td></td>
<td>Gingivostomatitis</td>
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<td></td>
<td></td>
<td>Respiratory</td>
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<td></td>
<td></td>
<td>Pneumonia</td>
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<td></td>
<td></td>
<td>Upper respiratory tract infection</td>
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<td></td>
<td></td>
<td>Croup</td>
</tr>
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<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viral or bacterial gastroenteritis</td>
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<tr>
<td></td>
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<td>Appendicitis</td>
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<tr>
<td></td>
<td></td>
<td>Neutropenic enterocolitis</td>
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<td></td>
<td></td>
<td>Perirectal abscess</td>
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<tr>
<td></td>
<td></td>
<td>Genitourinary</td>
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<td></td>
<td></td>
<td>Urinary tract infection/pyelonephritis</td>
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<td>Skin</td>
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<td></td>
<td></td>
<td>Abscess</td>
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<td>Cellulitis</td>
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<td>Erysipelas</td>
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<td></td>
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<td>Other</td>
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<td>Drug reaction</td>
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<td></td>
<td>Systemic viral infection</td>
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<td></td>
<td></td>
<td>Kawasaki disease</td>
</tr>
</tbody>
</table>

Many patients with a CVC presenting with fever will have had some contact with a medical provider prior to presentation to the ED. Patients being transported via emergency medical services should be assessed immediately. Vital signs should be closely monitored, and careful attention should be paid to the airway, breathing, and circulation in these patients. Supplemental oxygen therapy may be provided in the setting of clinical signs of sepsis or in the setting of respiratory distress or oxygen desaturation.

In patients with signs of sepsis or severe sepsis, additional intravenous access may be obtained if needed, and fluid resuscitation should begin prior to arrival to the ED. According to the Pediatric Advanced Life Support (PALS) guidelines, fluid resuscitation should begin promptly at the first recognition of sepsis, with a fluid bolus of 20 mL/kg of isotonic fluids (typically normal saline) given over 5 to 10 minutes. Up to 60 mL/kg can be given as needed within the first hour. Out-of-hospital care has been shown to improve inhospital processes and shorten the length of time to the initiation of antibiotics and intravenous fluids in the setting of patients presenting in sepsis or severe sepsis. 40,41

### Emergency Department Evaluation

#### History

A thorough history should be obtained, including evaluation of the onset, duration, and maximum height of the fever. Any prior administration and timing of antipyretics should be noted. History of erythema, tenderness, fluctuance, induration, or drainage at the catheter site should be elicited. 6 Ask about the caregivers’ perception of the child’s behavior in order to detect any alterations from the child’s baseline. Additional relevant symptoms that may help guide management should be ascertained by a complete review of systems.

It is important to know the type of CVC a patient has and when the catheter was placed. In patients who are immunocompromised and have an indwelling central catheter for the delivery of chemotherapy, ask when the patient last received chemotherapy and what type of chemotherapy was given. Certain chemotherapy protocols are more myelosuppressive, placing the patient at greater risk for neutropenia and overwhelming infection. 42 In patients known to be neutropenic, the duration of neutropenia is helpful to know, as the length of neutropenia correlates directly with risk of infection. 43,44 The patient’s type of malignancy is relevant, as leukemia and lymphoma—in contrast to solid tumors—have been identified as risk factors for bacteremia. 44,45 A history of chills or emesis may also...
suggest bacteremia in febrile neutropenic patients.46

Review the patient’s past medical history for previous central line infections, and what pathogens grew in the patient’s previous cultures, if known. In patients who report a history of recurrent central line infections, review any available microbiology results to identify multidrug-resistant organisms that may have grown in the past, especially recently. Relevant family history includes recurrent skin abscesses, infections, or known methicillin-resistant Staphylococcus aureus (MRSA) colonization or infections.

Physical Examination
A complete set of vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) should be obtained on every patient with a CVC presenting with fever. According to the International Pediatric Sepsis Consensus Conference, fever within 4 hours prior to arrival documented by a reliable source should be considered a true fever in pediatric patients who are afebrile on arrival.39 Any vital signs meeting criteria for SIRS should be noted, and patients with these criteria at presentation should be evaluated immediately.

A thorough examination is essential to uncover any potential source of fever. Look for meningeal signs and changes or alterations from baseline mental status. A thorough head, eyes, ears, nose, and throat examination includes examination of the tympanic membranes for signs of acute otitis media; looking inside the oropharynx for oral lesions, erythema, or exudates, and the lips for mucosal changes; examining the eyes for signs of conjunctivitis; and evaluating for sinus tenderness. Look for signs of increased work of breathing, and auscultate for any differences on lung examination that may suggest pneumonia, especially if the oxygen saturation level is low. Auscultation of the heart is also essential, and evidence of any new murmurs should be noted. Examine the abdomen for signs that may suggest pathology such as distension, absent bowel sounds, tenderness, rebound, or guarding. Inspect the catheter site for surrounding erythema, induration, fluctuance, or presence of discharge. Pay particular attention to signs of decreased perfusion such as delayed capillary refill time, cool extremities, diminished or bounding peripheral pulses, or changes in mental status.

Neutropenic patients may not mount the same inflammatory response as other patients. Therefore, consider investigating further even subtle examination findings in these patients.42 Pay particular attention to the mucous membranes for signs of mucositis or skin breakdown, as these place the patient at greater risk of bacterial translocation. Abdominal distension or tenderness should prompt further investigation for neutropenic enterocolitis or typhlitis. The perirectal area should be inspected for skin breakdown or evidence of perirectal abscess.

In some instances of severe neutropenia, perirectal abscess formation may not occur due to the low neutrophil count, and, therefore, tenderness may be the only sign of pathology in these patients.

In all patients with a CVC presenting with fever, serial examinations, including frequent measurement of vital signs, are essential to evaluate for any new findings, clinical changes, or evidence of clinical deterioration.

Diagnostic Studies
Blood Culture
A blood culture should be obtained prior to the initiation of antibiotic therapy in all patients with a CVC presenting with fever. However, this should not significantly delay antibiotic therapy. The Infectious Diseases Society of America recommends paired blood samples from both a catheter lumen and a peripheral vein. In a large prospective study of pediatric oncology patients with a CVC presenting with fever, 17% of true bloodstream infections were diagnosed in a culture from a peripheral vein when the paired culture from the CVC was negative.47 A similar retrospective study at a single institution also evaluated episodes of bacteremia that were diagnosed solely on the basis of peripheral culture. In this study, 318 episodes of bloodstream infections were included, of which 228 were classified as true bloodstream infections, and the remaining 90 cases were considered contaminants. Of the true bloodstream infections, 28 cases were detected solely from the peripheral blood culture when CVC and peripheral cultures were obtained within 24 hours of each other.48

Despite evidence to suggest the utility of both CVC and peripheral blood cultures, obtaining a peripheral blood sample is not always routine in many institutions, as it is deemed to be unpleasant for the patient. In cases when it is not possible to obtain a peripheral venous sample, 2 or more blood samples should be obtained from different catheter lumens if more than 1 lumen is present. When the colony count for the blood sample drawn from 1 lumen is at least 3-fold greater than the other lumen, the results may be considered a possible CR-BSI.49

A similar prospective study at a single institution also evaluated episodes of bacteremia that were diagnosed solely on the basis of peripheral culture. In this study, 318 episodes of bloodstream infections were included, of which 228 were classified as true bloodstream infections, and the remaining 90 cases were considered contaminants. Of the true bloodstream infections, 28 cases were detected solely from the peripheral blood culture when CVC and peripheral cultures were obtained within 24 hours of each other.48

Complete Blood Count
While the diagnosis of CA-BSI or CR-BSI is based upon culture results, a complete blood count (CBC) with differential should be obtained. Leukocytosis or leukopenia for age is 1 of the SIRS criteria and is
often routinely used as a diagnostic tool in the setting of concern for severe infection. In addition, any patient who is potentially immunocompromised or who is receiving chemotherapy should have a CBC with differential ordered to determine whether the patient is neutropenic (according to thresholds set by the institution) from their ongoing treatment. A CBC is also relevant in any patient presenting with signs of severe sepsis or septic shock, as blood products (including packed red blood cells and platelets) may be required in the initial resuscitation.

C-Reactive Protein
C-reactive protein (CRP) is a serum biomarker that is often measured in the setting of infection or when infection is suspected, and higher levels typically correlate with more-severe infection. CRP is an acute phase reactant that is released by the liver in the setting of inflammation within 4 to 6 hours of insult. CRP levels double every 8 hours and peak around 36 hours. Several studies have looked at the diagnostic value of CRP in the prediction of serious bacterial infection in pediatric patients. A prospective study by Pulliam et al looked at the diagnostic properties of CRP in the setting of clinically undetectable serious bacterial infection in patients aged 1 to 36 months. The results of the study showed that CRP was more sensitive and specific than white blood cell count or absolute neutrophil count in predicting serious bacterial infection in pediatric patients. A systematic review by Sanders et al looked at the diagnostic accuracy of CRP in detecting serious bacterial infection or bacterial versus viral infection in nonhospitalized infants and children. The results indicate that CRP has moderate value for ruling out serious bacterial infection but has minimal value in ruling out all bacterial infections. Additionally, the aforementioned studies provide information regarding the diagnostic utility of CRP in otherwise healthy patients presenting with fever, and it is unclear whether the presence of an indwelling catheter or a patient’s underlying disease process affect the utility of CRP studies.

Polymerase Chain Reaction
One study by Schachor-Mayheous et al looked at the molecular-based diagnosis of bacteremia in the setting of fever with or without neutropenia using the polymerase chain reaction (PCR) method for early detection of bacteremia. In the 148 blood cultures evaluated, the PCR method had a 48% sensitivity, but a 98% specificity for detecting bacteremia when compared to conventional culture results. The positive and negative predictive values were 86% and 89%, respectively. Although not as sensitive as culture in detecting all episodes of bacteremia, the study does demonstrate PCR’s utility in obtaining more-timely results and, in the event of a positive result, allows for the rapid ability to tailor antibiotic therapy to a specific pathogen.

Other Laboratory Testing
Although not directly predictive of infection, additional laboratory testing may assist in patient management and should be considered, particularly in the setting of sepsis. Urinalysis and culture are also recommended in neutropenic patients as long as a clean-catch urine sample can be obtained prior to institution of antibiotic therapy. In the presence of signs of local catheter site infection, a culture of any purulent drainage from the catheter site should be obtained. Many of the patient’s treatment medications may be nephrotoxic or hepatotoxic. A complete metabolic panel will evaluate for electrolyte abnormalities as well as kidney and liver dysfunction, as demonstrated by serum creatinine and transaminase levels, respectively. Adjustment of antibiotics may be necessary if renal or hepatic dysfunction is present. A blood gas with serum lactate level will evaluate for acidosis and aid in monitoring systemic perfusion. Any additional laboratory studies obtained should be based upon information gathered on the history or physical examination.

Imaging Studies
Imaging should be based upon history or physical examination findings, and should not be routinely ordered. Consider chest radiographs to evaluate for pneumonia if any symptoms such as tachypnea, respiratory distress, abnormal examination findings, or low oxygen saturations are present. When there is concern for catheter thrombosis or suppurrative thrombophlebitis, an ultrasound should be obtained. Identification of suppurrative thrombophlebitis is an indication for timely catheter removal.

In febrile neutropenic patients, abdominal imaging may be helpful if examination findings are subtle. When abdominal tenderness is present, consider abdominal radiographs or computed tomography scan to evaluate for neutropenic enterocolitis.

Treatment
Initial Resuscitation
Initial resuscitation should focus on the patient’s airway, breathing, and circulation. In the setting of sepsis or septic shock, oxygen should initially be provided via nasal cannula to maximize oxygen-carrying capacity. The decision to escalate respiratory support or to intubate patients within the setting of sepsis is based on a number of factors, including increased work of breathing, hypoventilation, and change in mental status. Therefore, close and continued evaluation of the respiratory status of these patients is imperative.

Circulatory status should be assessed, and fluid resuscitation should be initiated if hemodynamic abnormalities are present. Fluid resuscitation should begin within the first 60 minutes,
according to the PALS guidelines, with boluses of 20 mL/kg of crystalloid fluids given over 5 to 10 minutes. Boluses should be titrated to reversing hypotension, restoring normal heart rate for age, improving capillary refill time and peripheral pulses, increasing urine output, and improving mental status. Early reversal of hemodynamic abnormalities in pediatric patients with shock has been shown to greatly decrease mortality, regardless of the stage of abnormality at the time of presentation.57,58

**Antibiotics**

Prompt administration of empiric antibiotic therapy to a patient with a CVC is critical if bacterial infection is suspected. Time to antibiotic therapy of < 60 minutes has been associated with a lower rate of adverse outcomes in febrile neutropenic patients.1 The Surviving Sepsis Campaign also recommends administering empiric antibiotics within 60 minutes in patients presenting with sepsis. In a large retrospective study, delaying initial antibiotic therapy by > 3 hours from recognition of severe sepsis or septic shock was shown to be an independent risk factor for mortality in pediatric patients.59

The choice of antibiotic therapy should be based on several factors, including the patient’s underlying medical condition and reason for the CVC, history of previous positive culture results, and the institution’s antibiogram and susceptibility patterns. Empiric therapy with antibiotics having a broad spectrum of gram-positive and gram-negative effectiveness (such as vancomycin) should be initiated while awaiting culture results. The International Pediatric Fever and Neutropenia Guideline Panel recommends initial monotherapy with either an antipseudomonal beta-lactam or a carbapenem in neutropenic patients deemed to be high risk. In patients with a history of infection with a multidrug-resistant organism, a carbapenem should be initiated while awaiting culture results.57,60 The exact choice of antibiotic therapy in these patients should be based upon the local susceptibilities or individual medical center protocols. The addition of a second gram-negative agent (such as an aminoglycoside or carbapenem) should be reserved for unstable patients. In patients with a higher likelihood of gram-negative enteric organisms (such as patients with short gut syndrome), we recommend consideration of double antibiotic coverage for gram-negative organisms. In patients with a history of MRSA infection, skin colonization, or in centers with a high prevalence of MRSA infections, vancomycin should be considered as part of the empiric antibiotic regimen.60

If there is concern for toxic shock syndrome with fluid-refractory shock, clindamycin should be added for its antitoxin effects. Antibiotics should be administered through the indwelling catheter and alternated between lumens with each dose, if applicable. Routine initiation of antifungal therapy is not indicated in pediatric patients unless there is high clinical suspicion for fungal infection.6,11,56

Empiric antibiotics should be continued until culture results and antibiotic susceptibilities are available. In the event that only 1 blood culture is obtained, positive results may be difficult to interpret in some cases. For example, coagulase-negative *Staphylococcus* is a common skin micro-organism that is often a contaminant in blood cultures. However, it can also be pathogenic in patients with a CVC and cannot be determined to be a contaminant if only 1 blood sample drawn from 1 catheter lumen was found to be positive. If only 1 blood sample was drawn initially, a repeat sample should be drawn for culture, and empiric antibiotics continued while awaiting culture results.

When there is evidence of local catheter site infection, topical antibiotics may be sufficient if blood culture results are negative and there is no clinical concern for systemic infection. In the case of a tunnel infection or pocket infection, removal of the catheter and administration of systemic antibiotics are recommended.5,56

**Further Circulatory Management**

After aggressive fluid management and improvement in circulatory status, maintenance fluids should be initiated, if needed. If hepatomegaly or rales develop after the initial fluid boluses, these may be signs of fluid overload, and inotropic support should be initiated in lieu of additional fluid resuscitation. A chest x-ray should be considered to evaluate for pulmonary edema.

In the setting of fluid-refractory shock, inotropes should be initiated. In most cases of cold shock, which presents with cool extremities, diminished peripheral pulses, and delayed capillary refill time, dopamine is the inotrope that is typically initiated. Dopamine should be titrated to the goal of reversing the shock state. Epinephrine can be added if there is still evidence of a resistant shock state. For warm shock presenting with warm extremities, bounding peripheral pulses, and flash capillary refill time, norepinephrine is typically started and titrated to effect.56,57 In the setting of fluid overload, diuretics are not recommended until shock has resolved.

Resuscitation with blood products may be indicated in patients with anemia or thrombocytopenia. In the setting of severe sepsis or septic shock, it is recommended to transfuse packed red blood cells to keep the hemoglobin level > 10 mg/dL. Similarly, platelets are indicated in the setting of severe sepsis or septic shock if the patient’s platelet level is < 10,000/mcL or < 20,000/mcL with evidence of clinical bleeding.56
Clinical Pathway For Management Of Fever Or Suspected Infection In Pediatric Patients With A Central Venous Catheter

Patient with a CVC presents with fever or concern for infection

Concern for sepsis?

YES

NO

• Obtain blood cultures (at least 2 cultures from the CVC and a peripheral vein or from 2 different lumens), CBC with differential, and CRP (Class II)
• Culture any drainage from catheter (Class II)

NO

• Manage airway, breathing, and circulation with supplemental oxygen and isotonic fluid boluses (20 mL/kg over 5-10 min) up to 60 mL/kg in 1 hour (Class II)
• Obtain blood cultures (at least 2 cultures from the CVC and a peripheral vein or from 2 different lumens), CBC with differential, CRP, catheter site drainage culture, if indicated (Class II)
• Administer antibiotics within 60 min; consider whether patient is likely to be neutropenic, and double cover for gram-negative organisms if so (Class II)

Improvement in vital signs/reversal of hemodynamic abnormalities?

YES

NO

• Consider inotropes (Class II)
• Reassess airway and breathing; increase support as needed
• Consider blood products if Hgb < 10 mg/dL or platelets < 10,000/µL (Class II)
• Consider hydrocortisone (Class II)
• Reverse electrolyte abnormalities (Class II)

Admit patient to ICU (Class II)

History of MRSA or infection with resistant organism?

NO

YES

• Administer ceftriaxone (Class II)

Administer patient for continued antibiotics and close monitoring (Class II)

Consider discharge home with follow-up (Class II)

• Administer vancomycin
• Consider clindamycin if there is concern for toxic shock

Abbreviations: CBC, complete blood count; CVC, central venous catheter; CRP, C-reactive protein; Hgb, hemoglobin; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus.

Class Of Evidence Definitions

Each action in the clinical pathways section of Pediatric Emergency Medicine Practice receives a score based on the following definitions.

Class I
• Always acceptable, safe
• Definitely useful
• Proven in both efficacy and effectiveness

Level of Evidence:
• One or more large prospective studies are present (with rare exceptions)
• High-quality meta-analyses
• Study results consistently positive and compelling

Class II
• Safe, acceptable
• Probably useful

Level of Evidence:
• Generally higher levels of evidence
• Nonrandomized or retrospective studies: historic, cohort, or case control studies
• Less robust randomized controlled trials
• Results consistently positive

Class III
• May be acceptable
• Possibly useful
• Considered optional or alternative treatments

Level of Evidence:
• Generally lower or intermediate levels of evidence
• Case series, animal studies, consensus panels
• Occasionally positive results

Indeterminate
• Continuing area of research
• No recommendations until further research

Level of Evidence:
• Evidence not available
• Higher studies in progress
• Results inconsistent, contradictory
• Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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**Additional Therapies**

In patients in a persistent shock state despite appropriate fluid resuscitation and initiation of inotropes, administration of hydrocortisone should be considered. Shock doses range from 2 to 50 mg/kg/day of hydrocortisone.\(^6\) Electrolyte abnormalities should be corrected. In particular, glucose homeostasis is essential. Hypoglycemia should be diagnosed promptly and treated with a dextrose bolus. Significant hyperglycemia should be corrected using insulin therapy in conjunction with glucose infusion with a goal serum glucose level of < 180 mg/dL. Hypocalcemia should be reversed with intravenous calcium gluconate. Hypocalcemia can contribute to cardiac dysfunction and replacement should be considered, with care taken to avoid hypercalcemia.\(^5\)\(^7\)

**Considerations Following Initial Management**

After the initial resuscitation and stabilization, the patient’s primary subspecialty team should be contacted, as they may have additional knowledge of patient-specific information to aid in management. This is also particularly relevant when the patient presents to a hospital where he or she does not receive ongoing care. The primary subspecialty team may also have additional recommendations. Furthermore, collaboration with the primary care team is essential to ensure safe and appropriate disposition of the patient. In patients with a CVC with fever who have a clear source of infection unrelated to the catheter, treatment should be tailored specifically to the cause of the fever, although some would administer empiric broad-spectrum antibiotics until blood cultures are negative.

**Catheter Removal**

Immediate catheter removal is not necessary while awaiting culture results. Removal of a long-term indwelling catheter is recommended in the following situations of proven CA-BSI: severe sepsis or septic shock, suppurative thrombophlebitis, endocarditis, bloodstream infection that continues to produce positive cultures despite at least 72 hours of antibiotic therapy to which the organism is susceptible, or infections due to *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria. Catheter removal may also be necessary when it is infected with other less virulent (but difficult to eradicate) organisms, once contamination is ruled out by multiple positive blood cultures. If removed, the catheter tip should be sent for culture.\(^6\) Despite this recommendation, catheter removal may not be feasible in all pediatric patients, given the relative difficulty of obtaining alternative access, and this should be decided on an individual basis.\(^6\)\(^1\)\(^2\)

**Catheter Lock Therapies**

Catheter lock therapies have been proposed for use in conjunction with systemic antibiotics in the setting of CA-BSI. Several catheter lock therapies have been studied and include antibiotic locks, ethanol locks, hydrochloric acid locks, and urokinase. The substance is administered into the hub of the catheter and allowed to dwell for a period of time. The goal of catheter lock therapy is to reduce the incidence of treatment failure when catheter salvage is attempted by targeting difficult-to-eradicate biofilms that are attached to the catheter lumen.

The Infectious Diseases Society of America recommends antibiotic lock therapy in conjunction with systemic antibiotics in the setting of proven CA-BSI when catheter salvage is being attempted.\(^6\) Antibiotic concentrations needed to kill bacteria contained within a biofilm are 100 to 1000 times greater than concentrations that are required to kill free-floating bacteria. Antibiotic lock treatments can achieve this concentration within the catheter without systemic dissemination of the antibiotic. Studies have looked at the efficacy of antibiotic or other lock therapies in treating CA-BSIs when catheter salvage is attempted. The results have been varied and, therefore, there is insufficient evidence to strongly recommend catheter lock therapies in the setting of CA-BSI.\(^6\)\(^5\)\(^3\)

**Special Circumstances**

Neutropenic or otherwise immunocompromised patients deserve particular attention. The possibility of severe illness or clinical deterioration in these patients is much higher than in other patients with a CVC who present with fever or suspected infection. Prompt evaluation and administration of antibiotics or other necessary resuscitation are essential. As previously stated, subtle physical examination findings may be misleading, and all findings on examination should be investigated further. Communication with the patient’s primary subspecialty team will help with appropriate transition of care upon discharge or admission. Consider intensive care unit evaluation and admission if the patient is ill-appearing or has unstable vital signs.

**Controversies And Cutting Edge**

**Procalcitonin And Other Serum Biomarkers**

In children with a CVC presenting to the ED with fever, it is often difficult to distinguish between a viral etiology and bacterial etiology of fever. There has been significant investigation into the use of serum biomarkers to predict infection with viral versus bacterial pathogens, as well as to predict severity of disease.

Procalcitonin is a serum biomarker that has been studied as a potentially useful marker to predict serious bacterial infection in pediatric patients. Procalcitonin levels have been reported to rise within 3
to 4 hours in response to infection and reach plateau levels in 8 to 24 hours, making its use in the ED setting of particular interest. High concentrations of serum procalcitonin have been found in cases of neonatal sepsis and meningitis and in patients presenting with fever without an identifiable source.

In a study comparing procalcitonin versus CRP, interleukin-6, or interferon alpha for differentiation of viral versus bacterial infection, procalcitonin was found to predict serious bacterial infection better than the other serum biomarkers studied. A systematic review and meta-analysis of the role of procalcitonin in diagnosing severe infection in neutropenic pediatric patients presenting with fever found that CRP and procalcitonin had comparable diagnostic accuracy; however, procalcitonin was a more specific test for identifying bacterial sepsis when compared to CRP.

A study by Kasem et al looked at the diagnostic value of procalcitonin in the setting of pediatric patients with a CVC presenting with fever. The results of the study demonstrated that the procalcitonin level of patients with positive blood culture results was significantly higher than in patients with negative blood culture results. This was true in both neutropenic and non-neutropenic patients.

Results of a separate systematic review and meta-analysis of the value of serum biomarkers in predicting adverse outcomes in febrile neutropenic pediatric patients suggest that there is some improved predictive value of procalcitonin versus CRP in this population. However, there was significant heterogeneity among the results of the various studies used in the meta-analysis. Haeusler et al

Risk Management Pitfalls For Pediatric Patients With A Central Venous Catheter Presenting With Fever Or Suspected Infection (Continued on page 13)

1. “The patient was well-appearing in triage, so she didn’t need to be seen immediately.” All patients with a CVC presenting with fever should be evaluated upon arrival. In the setting of a CR-BSI, a patient’s clinical examination can change precipitously. Patients presenting with unstable vital signs should be triaged and evaluated immediately by an emergency clinician.

2. “The patient was tachycardic with fever, but he had a normal blood pressure, so we didn’t initially provide any fluid resuscitation.” In pediatric patients, hypotension is not required for a patient to meet the criteria for septic shock, and this is often a late finding. A patient with evidence of hemodynamic changes without hypotension is considered to be in compensated shock. Fluid resuscitation should be initiated promptly with the goal of reversing hemodynamic abnormalities such as tachycardia and hypotension, and normalizing urine output, mental status, and capillary refill time.

3. “We were having difficulty accessing the patient’s port, and the parents refused a peripheral blood culture, so the patient didn’t receive antibiotics for almost 2 hours.” It is recommended that blood cultures be drawn prior to the patient’s receiving antibiotics. However, since prompt antibiotic therapy has been shown to improve outcomes in neutropenic and critically ill patients, obtaining cultures should not significantly delay antibiotic therapy.

4. “We started antibiotic therapy within the first hour, but didn’t realize that the patient had a history of a previous infection with a multi-drug-resistant organism.” Timely and appropriate antibiotic therapy has been shown to improve outcomes in pediatric sepsis patients. It is important to consider each patient’s infection history and cover for resistant organisms if the patient has a history of a previous drug-resistant infection.

5. “The patient had a CVC and presented with fever, so blood cultures were drawn from 1 of 2 catheter lumens and empiric antibiotics were started 2 days ago. Even though the patient was still febrile after 48 hours, the culture results were negative, so we discontinued antibiotics.” A single culture from 1 lumen of the CVC has been shown in several studies to fail to diagnose bacteremia in some patients. Cultures should be drawn from the catheter and a peripheral vein or from all catheter lumens if a peripheral culture cannot be obtained. In the setting of a negative initial culture, repeat cultures should be obtained, and antibiotics should not be discontinued if clinical suspicion for bacteremia remains high.

6. “All patients with evidence of local catheter site infections should receive systemic antibiotic therapy.” When there is evidence of local catheter site infection, topical antibiotics may be sufficient if blood culture results are negative and there is no clinical concern for systemic infection.
Risk Stratification

There is considerable interest in the development of clinical risk prediction rules for febrile neutropenic pediatric patients. The guideline for management of children with fever and neutropenia suggests that each institution should adopt a validated risk stratification strategy that can be incorporated into clinical practice. However, there are several low-risk stratification schemas that have been developed and validated in different populations, making the uniform use of a single prediction rule unreliable. A study by West et al identified a temperature of ≥ 39.5°C and a capillary refill time of > 3 seconds to be associated with the need for critical therapies (defined as fluid resuscitation beyond 60 mL/kg, mechanical ventilation, or use of vasoactive medications). A systematic review and meta-analysis of conducted an updated systematic review and meta-analysis of the predictive value of biomarkers in the setting of fever and neutropenia in pediatric cancer patients. This study included an additional 13 studies that were published after the systematic review and meta-analysis published by Phillips et al. The results again demonstrated marked heterogeneity, making clinical conclusions regarding the utility of using serum biomarkers in the setting of pediatric neutropenia difficult. While procalcitonin appears to be a more specific marker for severe bacterial infection than CRP or other serum biomarkers, its utility in the initial diagnosis and management of febrile pediatric patients is still controversial and cannot be generalized to all patient populations.

Risk Management Pitfalls For Pediatric Patients With A Central Venous Catheter Presenting With Fever Or Suspected Infection

(Continued from page 12)

7. “The patient has a CVC and is febrile. He is also complaining of abdominal discomfort. We drew blood cultures and started antibiotics prior to admitting him to the general pediatric service.” The presence of a CVC does not mean that the source of the patient’s fever is always the catheter. In this case, a thorough examination would have revealed right lower quadrant tenderness and guarding, and prompted further evaluation for intra-abdominal pathology.

8. “The patient remained hypotensive after receiving a total of 60 mL/kg of normal saline in the first hour in addition to antibiotics. Dopamine was initiated; however, we had to titrate up on the dose due to persistent hypotension.” In patients with fluid refractory shock after appropriate resuscitation, inotropes should be started. If shock persists after the initiation of inotropic support with the appropriate escalation to additional inotropes as needed, hydrocortisone should be considered. Additional considerations include correcting electrolyte abnormalities and administering blood products if anemia or thrombocytopenia are present.

9. “An oncology patient with a port presented with a reported history of fever. We obtained a blood culture and CBC with differential and determined that the patient was not neutropenic. We gave him a dose of ceftriaxone and told him to follow up with his oncologist as needed.” Well-appearing, nonneutropenic patients with a CVC may not require admission to the hospital when presenting with fever. However, proper follow-up is essential. It is necessary to be in communication with the patient’s primary care service (ie, oncology) and ensure that there is timely follow-up of the cultures drawn. Furthermore, it should be confirmed that the patient will be able to return to the hospital in the event of a positive culture or clinical deterioration.

10. “The patient’s blood culture grew coagulase-negative staphylococci at 20 hours, and he was called back into the ED. He is well-appearing now, so we did not start antibiotics.” Coagulase-negative Staphylococcus is a common skin micro-organism that is often a contaminant in blood cultures. However, it can also be pathogenic in these patients, and it cannot be determined to be a contaminant if only 1 blood culture is drawn and found to be positive. Treatment should be continued until an additional blood culture can be drawn and determined to be negative.
the performance of risk prediction rules in children and young people with febrile neutropenia examined 8 different clinical decision rules. Only 2 studies in the systematic review included the presence of a CVC as part of the clinical decision rule. Of these 2 studies, only the “Ammann” rule was included in the meta-analysis portion of the study. The pooled data used in the study to examine this prediction rule showed high sensitivity to predict patients at low risk of serious bacterial infection (98%), but there was a low specificity of 13%.71

While individual institutions may have adopted an established clinical prediction rule or may have a protocol for stratifying high-risk versus low-risk febrile neutropenic oncology patients, it is important to keep in mind that the presence of a CVC may not be included in the risk stratification. Furthermore, while many studies have presented evidence of factors that may influence the risk of severe illness, this cannot replace individual clinical judgment.

**Disposition**

Most pediatric patients with a CVC presenting with fever will require admission for continued antibiotic therapy while awaiting blood culture results. In some cases, well-appearing oncology patients may be discharged home from the ED if timely and appropriate follow-up can be ensured, and if the patient is not neutropenic. A retrospective study by Kelly et al looked at the incidence of bacteremia in 167 febrile nonneutropenic oncology patients seen in the ED or outpatient clinic.18 Out of 459 visits, 29 cases of bacteremia were identified in the study. In all cases of bacteremia, patients received empiric antibiotics. Ninety percent of these patients were discharged home from the ED or clinic after receiving antibiotics, and 10% were admitted. All the patients who were discharged home were successfully called back when cultures resulted positive. There were no adverse outcomes reported in the discharged group.18 Another retrospective study looked at 138 nonneutropenic oncology patients with CVCs presenting to the ED or outpatient clinic with fever, or who were evaluated in the day-hospital while admitted for chemotherapy.72 A total of 392 episodes of fever in 138 nonneutropenic subjects were reviewed. Only 2.5% of patients received empiric antibiotic therapy. Of the 24 reported episodes of bacteremia in the study, only 10 cases were admitted from the ED due to ill appearance or complication with the line. Of the remaining patients, 7 were sent home without receiving empiric antibiotics and were later called back to the ED for a positive culture, 5 cases grew out during the day-hospital admission for chemotherapy, and 2 were considered contaminated and the patients were not treated. None of the patients discharged home and called back for a positive culture had a reported adverse outcome.72 These studies suggest that it is possible that some nonneutropenic oncology patients with a CVC presenting with fever may be discharged with close follow-up. However, these studies are insufficiently powered to make definitive conclusions, and institutional protocols should be established to guide the emergency clinician.

Neutropenic oncology patients will require admission and continued empiric antibiotic therapy and monitoring, as they have a higher risk for clinical deterioration due to sepsis. Other patient populations may require hospitalization based on their comorbidities or underlying medical conditions, which make them more susceptible to severe infection. Pediatric patients with intestinal failure, for example, can be considered relatively immunocompromised due to chronic malnutrition. They also have alterations in the integrity of the gastrointestinal tract, making them more susceptible to infection. The standard of care is often to admit these patients to the hospital while awaiting blood culture results.73 Similarly, patients receiving hemodialysis because of end-stage renal disease are also relatively immunocompromised and are at increased risk for serious bacterial infection and other complications.

Patients with severe sepsis or unstable vital signs, or patients who require aggressive fluid resuscitation or other interventions should be admitted to the intensive care unit for critical care therapy and closer monitoring.18 For additional information on the management of septic shock, see the April 2015 *Pediatric Emergency Medicine Practice* issue titled

**Time- And Cost-Effective Strategies**

- Patients with a CVC presenting with fever should be evaluated promptly, and antibiotics and other resuscitative measures should be administered within the first hour.
- The routine use of imaging is not indicated in most patients with a CVC presenting with fever. Imaging should be ordered selectively based on history and physical examination.
- Well-appearing, nonneutropenic oncology patients with a CVC may not require admission when they present with fever if appropriate follow-up can be ensured.
- Developing protocols to standardize the triage and immediate evaluation of these patients may save both time and money, and may improve the quality of care delivered.
- Early consultation with subspecialty services may improve the time to definitive treatment and disposition.
In pediatric patients with a CVC presenting with fever, it is often difficult to distinguish between catheter-associated infections and fever unrelated to the catheter. A thorough history and physical examination is essential to uncover any potential sources of fever. Empiric broad-spectrum antibiotic therapy should be administered after blood cultures are obtained. It is important to consider individual patient-related factors such as any underlying disease process and any history of previous microbiologically proven infections when choosing appropriate empiric antibiotic therapy. In patients presenting with signs of sepsis or patients who are otherwise unstable, early resuscitation with the goal of prompt reversal of hemodynamic abnormalities has been shown to improve outcomes. Catheter removal is typically not necessary in the immediate setting and should be decided on an individual basis. Consultation with the patient’s primary care subspecialty service is important for current and subsequent management.

**Case Conclusions**

Upon initial evaluation, the 8-year-old patient with acute lymphoblastic leukemia was ill-appearing but nontoxic. Physical examination revealed evidence of oral mucositis. The remainder of the examination was unremarkable. A blood culture was obtained from his port as well as a CBC with differential and a CRP. Given the increased risk of gram-positive organisms in the presence of mucositis, he was empirically started on cefepime and vancomycin per institutional protocol. The results of the CBC demonstrated an absolute neutrophil count of 10 cells/mcL, hemoglobin of 6.4 mg/dL, and a platelet count of 100,000/mcL. The patient’s CRP level was 2.5 mg/L. You administered a total of 40 mL/kg of normal saline for tachycardia and transfused 10 mL/kg of packed red blood cells. Given the patient’s history of cough prior to presentation, a chest radiograph was obtained, but showed no evidence of acute infiltrate. After initial resuscitation and antipyretics, the patient’s fever resolved, and his vital signs improved. Subsequent evaluation revealed no change in his clinical status, and you admitted him to the general oncology unit for continued antibiotic therapy.

Upon evaluation, the 4-year-old patient with gastrochisis appeared clinically dehydrated. You administered 220-mL/kg normal saline boluses. You ordered a CBC, and the results were within normal range for her age. You also ordered a CRP, which was 1.5 mg/L. You obtained a blood culture from both lumens of her Broviac line. Given her history of multiple resistant organisms and history of recent MRSA line infection, you started her on meropenem and vancomycin, and admitted her to the pediatric floor for further management.

**References**

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study will be included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.


11. Bourgeois FC, Lamagna P, Chiang VW. Peripherally inserted...
(Review)

(Review)

(Review)

(Case control study; 473 patients)

(Prospective study; 252 patients)

(Prospective study; 178 patients)

(Prospective study; 281 patients)

(Prospective cohort study; 167 patients)

(Review)

(Review)

(Retrospective review; 587 patients)

(Review)

(Prospective study; 378 patients)

(Retrospective cohort study; 80 patients)

(Prospective study; 59 patients)

(Prospective study; 152 patients)

(Prospective study; 9 patients)

(Retrospective review; 101 patients)

(Prospective study; 16 patients)

(Observational study; 47 patients)

(Retrospective review; 18 patients)

(Retrospective chart review; 44 patients)

(Retrospective review; 39 patients)

(Review)

(Editorial commentary)

(Practice guidelines)

(Review)

(Review)

(Consensus statement)

(Prospective study; 963 patients)

(Prospective observational study; 45,394 patients)

(Review)

(Prospective chart review; 52 patients)

(Retrospective cohort study; 13 patients)

(Retrospective review; 161 patients)

3. A 13-year-old girl with a CVC for acute myeloid leukemia presents with fever and altered mental status. Her vital signs are: temperature, 40°C; heart rate, 180 beats/min; respiratory rate, 40 breaths/min; blood pressure, 90/30 mm Hg; and pulse oximetry, 88%. She has no evidence of airway obstruction, but she is lethargic and poorly responsive to questions. Which of the following should be the initial management?
   a. Application of oxygen via facemask
   b. Administration of 1 L normal saline intravenous fluid bolus
   c. Administration of dopamine 20 mcg/kg/min
   d. Obtaining blood cultures from her CVC and a peripheral vein
   e. Empiric administration of cefepime

4. A 4-year-old boy with acute lymphoblastic leukemia presents to the ED with a temperature of 38.1°C, cough, and rhinorrhea. He has a port, and a CBC drawn earlier in the day noted an absolute neutrophil count of 3500/mm³. He is well-appearing, with no signs of pneumonia. Which of the following antibiotic choices is most appropriate for empiric treatment?
   a. Ceftriaxone
   b. Cefepime
   c. Cefazolin
   d. Cephalexin
   e. Vancomycin

5. A 7-year-old boy with short gut syndrome presents to the ED with a temperature of 39°C. He has a Hickman® catheter. His heart rate is 170 beats/min, and his blood pressure is 80/40 mm Hg. He has a history of recurrent CA-BSI, but his mother is unsure of his recent culture results. Which of the following antibiotic choices is most appropriate for empiric treatment?
   a. Ceftriaxone and clindamycin
   b. Clindamycin and cefepime
   c. Cefazolin and oxacillin
   d. Cefepime and meropenem
   e. Vancomycin and meropenem

6. A 3-year-old boy with acute lymphoblastic leukemia presents to the ED with a temperature of 39.2°C. He has a Hickman® catheter, and a CBC drawn earlier in the day noted an absolute neutrophil count of 150/mm³. He is well-appearing, and the rest of his vital signs are normal. Which of the following antibiotic choices is most appropriate for empiric treatment?
   a. Ceftriaxone
   b. Cefepime
   c. Cefazolin
   d. Cephalexin
   e. Vancomycin
7. A 12-year-old girl with lymphoma currently receiving chemotherapy via a CVC was seen in the ED 2 days ago for fever. The patient’s blood culture grew coagulase-negative staphylococci at 36 hours and she was called back to the ED. She is well-appearing now, with a temperature of 37.9°C, heart rate of 105 beats/min, and normal blood pressure. She is not neutropenic. Management should be:
   a. Admission for intravenous vancomycin
   b. Admission for intravenous meropenem
   c. Admission for intravenous meropenem and oxacillin
   d. Discharge to home after administration of intravenous ceftriaxone
   e. Repeat blood culture and discharge to home without antibiotic therapy

8. An 18-month-old boy with acute lymphoblastic leukemia presents with a temperature of 39°C. In addition to a CBC and blood culture, which of the following tests would be most useful to predict serious bacterial infection in this patient?
   a. Erythrocyte sedimentation rate
   b. CRP
   c. Procalcitonin
   d. Interleukin-6
   e. Interferon alpha

9. Which of the following patients with a CVC presenting with fever are candidates for outpatient management? Each is well-appearing with normal vital signs.
   a. A 10-year-old with end-stage renal disease dependent on hemodialysis
   b. A 5-year-old with short gut syndrome with a Broviac® catheter, dependent on parenteral nutrition
   c. A 3-year-old with intestinal failure with a Hickman® catheter, dependent on parenteral nutrition
   d. An 18-year-old with acute lymphoblastic leukemia who is neutropenic and has a port
   e. A 13-year-old with osteosarcoma with an absolute neutrophil count of 1600/mm³ and a Hickman® catheter
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**Goals:** Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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Pediatric Emergency Medicine Practice (ISSN Print: 1549-9650, ISSN Online: 1549-9669, ACID-FREE) is published monthly (12 times per year) by EB Medicine. 5550 Triangle Parkway, Suite 150, Norcross, GA 30092. Phone: 1-800-249-5770 or 678-366-7933 Fax: 1-770-500-1316. E-mail: ebm@ebmedicine.net Website: ebmedicine.net

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