CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTION IN CHILDREN: AN UPDATE ON TREATMENT

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Long-term central venous catheters (CVCs) are essential for modern pediatric practice. These devices terminate in a large central vein, usually the superior vena cava, and are used for administration of drugs, fluids and blood products; for blood collection and for hemodialysis. The most common, serious complication of CVC use is central line–associated bloodstream infection (CLABSI). Rates of CLABSI vary widely according to device type and patient population and can range from approximately 0.2 episodes per 1000 catheter-days in children with sickle cell disease to 11 per 1000 days in infants with intestinal insufficiency.1,2

The most common infecting organisms are coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), *Staphylococcus aureus*, *Klebsiella* spp., *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., other enteric Gram-negative bacteria and *Candida* spp. Microorganisms are introduced predominately through the hub during routine use or at the time of catheter insertion. After the first 14 days, intraluminal colonization is the most important source of infection.3 Important consequences of CLABSI include extended hospital stay (median of 12 days in 1 study), interruption of chemotherapy or other treatment, catheter removal (up to 50% of episodes), intravascular thrombosis, endocarditis, sepsis (up to 10%) and rarely death.4,5

Techniques to prevent CVC colonization during insertion, such as maximum sterile barrier precautions, reduce the risk of CLABSI. After insertion, appropriate CVC dressings, careful catheter access technique, alcohol catheter caps and the use of prophylactic lock therapy with taurodilidone, antibiotic or preservative-containing heparin solution can reduce the risk of infection in some groups.6–9

This review focuses on the management of CLABSI in children, outside the neonatal period, who have long-term tunneled CVCs (eg, Broviac or Hickman catheters, Bard Access Systems, Salt Lake City, Utah) or implantable ports (eg, Port-A-Cath, Smiths Medical, Dublin, Ohio). Major controversies include duration and choice of systemic antibiotic therapy, indications for catheter removal, screening for complications and the roles of adjunctive treatment and secondary prevention techniques. This review assesses the available literature and identifies pragmatic treatment strategies based on the best available evidence basis. The Infectious Diseases Society of America guidelines, which focus predominantly on adult patients, are referenced where a consensus recommendation is required but evidence is limited or conflicting.

**DIAGNOSIS AND DEFINITIONS**

The classic presentation of CLABSI is the development of fever and chills immediately after accessing a catheter that has been locked for some time. However, the range of clinical presentations is broad, and the catheter may not always be immediately considered as the source of fever. Most episodes are not associated with any visible abnormality at the site of the catheter.3

Unless an alternative source is identified, all bloodstream infections in patients with a CVC are classified as CLABSI. This surveillance definition may overestimate the true number of infections that are attributable to the CVC. Therefore, when there is evidence to confirm that the colonized device is the true source of infection, the more specific diagnosis of catheter-related bloodstream infection (CRBSI) is used (Fig. 1).10 Confirmatory tests include culture of the catheter tip, quantitative blood cultures or differential time to positivity (DTP) of blood cultures drawn from different sites. Data from pediatric oncology patients suggest that up to one third of CLABSI episodes are related to infections at other sites and are therefore not CRBSI.10

Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal or adjunctive therapy. CVC tip culture can identify CRBSI, but precludes salvage of the catheter.

The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP between blood cultures drawn from the catheter and from a peripheral vein or separate lumen. In cases of true CRBSI, blood obtained through a colonized lumen will usually indicate growth
before uncolonized lumens or peripheral blood because of high intraluminal microorganism burden. To apply, identical volumes of blood must be collected for culture simultaneously from each site, and a continuously monitored blood culture system is needed. In pediatric oncology patients who had simultaneous peripheral and central cultures, a DTP of ≥150 minutes had a specificity of 100% and sensitivity of 89% for CRBSI. For cultures from both lumens of a double-lumen catheter, a DTP of ≥180 minutes had a specificity of 94% and sensitivity of 61%. These data suggest that DTP can be confidently used to diagnose CRBSI, but that the negative predictive value is poor, especially when comparing 2 lumens of a double-lumen catheter.

To maximize the sensitivity and specificity of diagnosis in cases of suspected CRBSI, blood cultures should be collected from the catheter and from the peripheral blood before initiation of antibiotics. Blood should generally be collected from all lumens of a multilumen catheter (although there is an absence of data to support this consensus recommendation), as some can be uncolonized. Similarly, in patients with a single-lumen catheter, at least 2 sets of blood cultures should be collected through the CVC if a peripheral culture is not taken. Normal skin flora are the most common causes of CLABSI and are also frequent blood culture contaminants. Therefore, definitive diagnosis of bloodstream infection with a common skin contaminant requires multiple positive cultures to exclude the possibility of contamination during collection or inoculation. If multiple blood cultures have not been collected before antibiotics, a presumptive diagnosis of CLABSI has to be made, leading to unnecessary treatment in cases where the positive culture has resulted from contamination.

Peripheral blood should be collected in all cases of suspected CLABSI before antibiotics are started, but pediatrics often avoid this. There are a number of important situations in which peripheral blood culture aids management. One example is a patient with severe sepsis in whom catheter removal might limit venous access and compromise treatment. Another is attempted catheter salvage complicated by persistent bacteremia during appropriate antibiotic therapy in which evidence that the catheter is not the primary focus could lead to earlier identification of an intravascular focus such as endocarditis. Lastly, definitive diagnosis of CRBSI can support a decision to remove and replace a catheter in cases of S. aureus or candida infection. All these situations can be difficult to predict at initial presentation.

After diagnosis of CLABSI, blood cultures should be collected daily until cultures from all lumens are negative. Further peripheral cultures may not be necessary if blood can be collected from all lumens of the catheter and the patient is clinically stable.

**Diagnosis of Complications Resulting From CLABSI**

Complicated catheter-associated infections include tunnel or port pocket infection, endovascular infections such as endocarditis or supplicative thrombophlebitis and metastatic infections such as osteomyelitis and liver, spleen or brain abscess. Catheter-related skin and soft tissue infection can be identified by localized erythema, tenderness, fluctuance or swelling. An intravascular focus may be identified when there is persistent bacteremia or fungemia after CVC removal, despite appropriate antimicrobial therapy. Clinical signs, such as new murmur, peripheral stigmata and cardiac failure or localized tenderness and swelling of a limb, are often absent in infective endocarditis and supplicative thrombophlebitis, respectively.

**CATHETER SALVAGE**

Catheter salvage is attractive in many cases because of the cost and inconvenience of replacement. However, catheter removal substantially reduces the risk of relapse, persistent bacteremia or fungemia, and metastatic infection. The risk of relapse differs by device and organism. For ports, the risk may be >50%, probably related to the complex structure and high internal surface area of the port housing.

Salvage should not be attempted if the catheter is no longer essential for clinical care. Timely removal of the CVC is also indicated for infections complicated by sepsis, tunnel or port pocket infection, endocarditis or supplicative thrombophlebitis, relapse of CLABSI with an identical organism, and infection with mycobacteria, fungi such as Candida spp., S. aureus, Bacillus cereus and some multiresistant bacteria. With attempted catheter salvage, candida and mycobacteria CRBSIs have treatment failure rates over 70%, and S. aureus and B. cereus infections have relapse rates around 50% with potentially catastrophic complications. The catheter should therefore be removed in all the above cases, except where replacement will be so difficult that the high risk of treatment failure is considered justifiable.

It is appropriate to consider catheter salvage in other patients in view of the relatively high success rates of salvage therapy and potential hazards of CVC replacement. Catheter replacement is costly, carries risks associated with anesthesia and local trauma, does not reduce the risk of new CLABSI (the risk may actually be increased immediately after replacement) and venous occlusion can preclude future use of that insertion site. If salvage is attempted, the patient should be closely observed for the development of acute complications, persistent infection or sepsis. The catheter should be removed if complications develop or if bacteremia or fungemia persists after 72 hours of appropriate antibiotic therapy.

After catheter removal, reinsertion of a new long-term CVC should ideally be delayed until blood cultures collected after removal are negative to prevent immediate contamination of the new device. This delay might be unnecessary for patients in whom clearance of bacteremia or fungemia is documented before catheter removal. The absolute
risk of contamination of the new device is unknown in either case, so the decision of whether to delay reinsertion should take into account the potential clinical impact of either delayed reinsertion or colonization of the new catheter. The use of guidewire catheter exchange in the management of CLABSI is controversial. The technique has the benefit of reducing venous occlusion and mechanical complications of new device insertion, but it may be associated with contamination of the new catheter and can be technically difficult in young children.13 Guidewire replacement with an antimicrobial impregnated catheter could potentially be beneficial to prevent colonization of the new device. One retrospective study of nontunneled impregnated devices reported excellent outcomes, but there are no prospective studies supporting the method, and appropriate devices for tunneled use are not yet available.19

### SYSTEMIC ANTIBIOTIC THERAPY

Empiric antibiotic therapy for suspected CLABSI should take into account the clinical condition of the patient, documented past colonization or infection with resistant organisms, known allergies and local resistance patterns. Initial therapy should usually be with vancomycin combined with a broad-spectrum agent active against Gram-negative bacteria including *Pseudomonas aeruginosa*, such as an aminoglycoside (eg, gentamicin), and antipseudomonal penicillin (eg, piperacillin-tazobactam), or a cephalosporin (eg, ceftazidime or cefepime). If multiresistant Gram-negative infection is likely, the use of a carbapenem (eg, meropenem) should be considered. In patients with clinical sepsis, an additional third agent of a different antibiotic class with activity against Gram-negative bacteria is recommended, until susceptibility results are available because of the risk of resistance. Although evidence is limited, it seems logical to administer therapy through all lumens of the CVC by splitting or rotating doses. Empiric therapy for fungal infection is not routinely recommended except in high-risk patients; considerations include severity of illness and presence of multiple risk factors for candidemia, such as prolonged intensive care unit stay, administration of total parenteral nutrition, immunosuppression, prolonged antibiotic exposure, previous candidemia without catheter removal and known candida colonization.20

Once the causative organism is identified, targeted therapy should be selected based on susceptibility testing. Ideally, a single narrow spectrum agent should be used. If the catheter is retained, patients should receive 10–14 days of pathogen-specific systemic antibiotic therapy from the date of the first negative blood culture through each lumen of the catheter.13 A longer duration of therapy is indicated for cases complicated by endocarditis, suppurative thrombophlebitis or metastatic infection. Use of antibiotics, that have superior in vitro activity against biofilm bacteria, such as ciprofloxacin and rifamp(inc) in, has been proposed to potentially offer a greater chance of eradication of infection, but there is currently no evidence that these drugs improve clinical outcomes. Rifampin should not be used as a single agent for the treatment of infection due to rapid development of antibiotic resistance.

If the catheter is removed, patients should receive 10–14 days of appropriate systemic therapy. Oral therapy may be considered if an appropriate drug is available and intravenous access is difficult to maintain.21 A shorter 5- to 7-day treatment course is reasonable for CLABSI due to coagulase-negative staphylococci if the catheter is removed and blood cultures clear promptly.13 There is no evidence to support the use of synergistic aminoglycoside in the absence of endocarditis.

### TREATMENT FAILURE

Despite appropriate antibiotic therapy, treatment failure (persistent bacteremia, premature device removal due to infection or relapse of infection) occurs in at least 25% of CLABSI episodes in which salvage is attempted. Relapse can occur many months after infection.20 Failure is highest in infections caused by certain organisms (such as *S. aureus*, *Candida* spp., *Bacillus* spp. and mycobacteria), tunnel and pocket infection, and in ports.13 This is attributable to biofilm, organized communities of microorganisms in a sessile state, predominantly on the luminal surface of the catheter. Mechanisms of treatment failure are described in Figure 2.27 In addition to the risk of treatment failure,
prior CLABSI increases the risk of future episodes. This might be associated with line-care technique, biofilm or catheter-associated thrombus acting as a nidus for reinfection, or the presence of multispecies biofilm.

CATHETER LOCK THERAPY

Catheter lock therapy (CLT) may be used in addition to systemic therapy with the aim of reducing treatment failure by targeting biofilm bacteria. A small dose of antimicrobial agent is instilled to fill the catheter lumen (usually ≤1.5 mL) and is allowed to dwell for an extended period of time (usually hours to days). This permits high concentrations of antimicrobial agent at the site of infection and can be repeated in each lumen throughout the course of antibiotic treatment. For example, local vancomycin concentrations of up to 5 mg/mL, 1000 times higher than the usual minimum inhibitory concentration, are achievable. This targets intraluminal colonization and would not be expected to improve outcomes for extraluminal colonization or infected catheter-associated thrombus. Specific agents used for CLT are outlined below.

Antibiotic lock therapy (ALT) with vancomycin, daptomycin, ceftriaxone, amikoglycosides, ciprofloxacin and other agents, individually or in combination, have been reported. Published studies on ALT are heterogeneous and mostly nonrandomized. One randomized study of vancomycin or cefazidine lock therapy in addition to systemic antimicrobial therapy showed a nonsignificant trend in the reduction of treatment failure (33% versus 57%; \( P = 0.1 \)) and relapse of infection (14% vs 39%; \( P = 0.06 \)) in the treatment group. In adults, ALT seems to be well-tolerated with few adverse effects reported. Infectious Diseases Society of America treatment guidelines for CLABSI recommend the routine use of adjunctive ALT for adults and children. However, the uptake of ALT use in pediatric practice seems to be inconsistent. This may be related to concerns about the development of antibiotic resistance, a paucity of pediatric safety data, the potential for heparin overdose in infants, the need for prolonged dwell times and the lack of commercially available lock solutions. Antibiotic solutions for ALT are produced extemporaneously and usually admixed with heparin to prevent catheter occlusion. Recommended heparin concentrations vary from 0 to 5000 units/mL depending on the antibiotic, but high concentrations are contraindicated in small infants due to the risk of systemic anticoagulation. More data are needed before a strong recommendation can be made on the routine use of adjunctive ALT in pediatrics, and ALT should not be considered mandatory in children.

Ethanol lock therapy (ELT) for the treatment of CLABSI has not been studied in published randomized trials. Ethanol penetrates biofilm and rapidly kills microorganisms, including common CLABSI pathogens such as *S. aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, *P. aeruginosa* and *Candida* spp., by protein denaturation. In vitro studies suggest that maximum killing occurs during the first 2 hours of exposure to 70% ethanol. One single-center retrospective review of pediatric oncology patients treated with and without ELT has been reported, which demonstrated a reduction in treatment failure, although this was not statistically significant. The small sample size and study design make these results difficult to apply broadly. Successful treatment of candida CRBSI using ELT has been reported in an uncontrolled series. This is interesting because of the historically poor outcomes of these infections. Other retrospective studies are uncontrolled and do not provide information about efficacy of the treatment.

<table>
<thead>
<tr>
<th>TABLE 1. The Bottom Line: Recommendations and Areas of Uncertainty for the Management of CLABSI in Children</th>
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<tr>
<td><strong>Diagnosis</strong></td>
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<tr>
<td>• Blood cultures should be collected from at least 2 sites before initiation of antibiotics (ideally from all lumens of a multilumen CVC).</td>
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<td>• Peripheral blood culture should be collected when possible.</td>
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<td>• Differential time to positivity may help identify true catheter-related bloodstream infection.</td>
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<td><strong>Catheter Salvage</strong></td>
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<tr>
<td>• The CVC should be removed if:</td>
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<tr>
<td>○ It is no longer required for routine care;</td>
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<tr>
<td>○ Sepsis, tunnel or port pocket infection, endocarditis or suppurative thrombophlebitis are present;</td>
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<tr>
<td>○ The infection is with mycobacteria, Candida spp. or other fungi, <em>Staphylococcus aureus</em>, <em>Bacillus cereus</em> or some multiresistant bacteria.</td>
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<tr>
<td>• Catheter salvage is reasonable in other cases, but should be abandoned if complications develop, if there is persistent bacteremia after 72 hours or if the infection relapses after cessation of antibiotics.</td>
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<td><strong>Systemic Antibiotic Therapy</strong></td>
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<td>• Patients with CLABSI should receive 10–14 days of appropriate antibiotic therapy from the date of the first negative blood culture.</td>
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<td>• Longer therapy is warranted in cases of fungemia, endocarditis, suppurative thrombophlebitis or metastatic infection.</td>
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<tr>
<td>• If the catheter has been removed, shorter treatment may be appropriate in infections due to coagulase-negative staphylococci, but other organisms should be treated for 10–14 days.</td>
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<td><strong>Adjunctive Therapy</strong></td>
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<tr>
<td>• Antibiotic lock therapy may be reasonable as adjunctive treatment for CLABSI.</td>
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<tr>
<td>• Other catheter lock therapies (CLT), such as ethanol, hydrochloric acid or taurolidine, should not be routinely used for the treatment of CLABSI.</td>
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<tr>
<td><strong>Some Areas of Uncertainty</strong></td>
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<tr>
<td>• What is the optimal duration of antibiotic therapy for uncomplicated CLABSI if the catheter is removed or it is retained?</td>
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<tr>
<td>• Does splitting or rotating antibiotic doses through all lumens of the CVC reduce treatment failure?</td>
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<tr>
<td>• Are biofilm-active antibiotics more effective than other antibiotics for the treatment of CLABSI?</td>
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<tr>
<td>• Is CLT with ethanol, antibiotics, taurolidine or another solution beneficial in routine treatment of CLABSI?</td>
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<tr>
<td>• Is secondary prophylaxis with CLT beneficial in routine management of CLABSI?</td>
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<tr>
<td>• Should catheter reinsertion be delayed after removal of a CVC for infection?</td>
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<tr>
<td>• Can a colonized CVC be safely replaced with an antimicrobial impregnated device by guidewire exchange?</td>
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<tr>
<td>• Can ultrasound identification of asymptomatic catheter-associated thrombus help guide therapy for CLABSI?</td>
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complications (38% versus 19%; \( P = 0.3 \)). The available data do not support the use of hydrochloric acid lock therapy for the treatment of CLABSI.

CARDIAC AND VASCULAR IMAGING

Suppurative Thrombophlebitis

Suppurative thrombophlebitis, the presence of infected intravascular thrombus, requires catheter removal and prolonged therapy (4–6 weeks), as well as anticoagulation in many cases. However, the routine use of imaging to screen for catheter-associated thrombosis in the absence of clinical symptoms may be misleading. One prospective study found intravascular thrombus in 71% of all patients with CLABSI due to \( S. aureus \), many of whom had no local signs of this, but the clinical impact of such asymptomatic blood clots is unknown. Another study used ultrasound to screen for catheter-associated thrombosis in all CLABSI episodes in adult patients with acute leukemia. Catheters were removed from patients with evidence of catheter-associated thrombus. The study reported that death from sepsis and catheter loss was less common in the intervention group compared with historical controls, but the study has a number of methodological problems and no children were included.

Therefore, at present, venous imaging is recommended only when there are signs and symptoms of thrombosis or persistent bacteremia or fungemia after 72 hours of appropriate antibiotic therapy and catheter removal. Appropriate management of incidentally diagnosed, nonvenoocclusive, catheter-associated thrombus remains unclear; however, catheter removal with delayed reinsertion and consultation with a pediatric hematologist may be warranted.

Endocarditis

Patients with persistent unexplained bacteremia or fungemia >72 hours after appropriate antibiotic treatment and catheter removal and those with significant structural cardiac disease are at high risk of endocarditis. If patients have risk factors or have clinical signs of endocarditis, then echocardiography and consideration of empiric endocarditis therapy are warranted. Adults with \( S. aureus \) CLABSI have a high risk of concomitant endocarditis, and so empiric treatment or presumptive exclusion of endocarditis by transesophageal echocardiography has been recommended. However, the risk of endocarditis associated with \( S. aureus \) CLABSI seems to be much lower in children without specific risk factors (~3%). Children without preexisting cardiac risk factors who develop \( S. aureus \) CLABSI therefore do not require routine echocardiography in the absence of clinical signs of endocarditis or unexplained prolonged bacteremia.

SECONDARY PREVENTION

The long-term risk of CLABSI is increased in children with prior episodes. Patient or caregiver education and careful attention to catheter care and access techniques may help prevent future episodes and should be provided in all cases. The use of heparin with preservatives reduces the risk of CLABSI, but benzyl alcohol should be avoided in newborn infants. In addition, specific secondary prevention, such as prophylactic ethan-ol, antibiotic or taurolokin lock therapy, may be beneficial, but there is no evidence for these specifically as secondary prophylaxis.

LOOKING AHEAD

Potential future CLABSI treatments include phage therapy, nanoparticles and other agents, which are directed against biofilm structural elements (eg, proteolytic enzymes and surfactants), are active against organisms within biofilm (eg, taurolokin, metal chelators and pilus synthesis inhibitors) or interfere directly with bacterial biofilm regulation (eg, nucleotide second messenger systems). It is unclear which of these will progress to human trials.

CONCLUSIONS

Despite the development of preventive measures to reduce risks of infection related to CVC insertion and maintenance, CLABSI continues to be a significant burden in pediat-ric populations. Current treatments have a high failure rate predominantly due to relapse and reinfection because of the difficulty in preventing and eradicating intraluminal biofilm. Some adjunctive therapies are likely to be beneficial, but current evidence to support these is limited. More research is needed to determine the optimal management of CLABSI in children and adolescents.

REFERENCES


