CRITICAL CARE

REVIEW

Bench-to-bedside review: Challenges of diagnosis, care and prevention of central catheter-related bloodstream infections in children

Susanne Janum[1], Walter Zingg[2], Volker Classen[3] and Arash Afshari*[3,4]

Abstract

Central venous catheters (CVCs) are indispensable in modern pediatric medicine. CVCs provide secure vascular access, but are associated with a risk of severe complications, in particular bloodstream infection. We provide a review of the recent literature about the diagnostic and therapeutic challenges of catheter-related bloodstream infection (CRBSI) in children and its prevention. Variations in blood sampling and limitations in blood culturing interfere with accurate and timely diagnosis of CRBSI. Although novel molecular testing methods appear promising in overcoming some of the present diagnostic limitations of conventional blood sampling in children, they still need to solidly prove their accuracy and reliability in clinical practice. Standardized practices of catheter insertion and care remain the cornerstone of CRBSI prevention although their implementation in daily practice may be difficult. Technology such as CVC impregnation or catheter locking with antimicrobial substances has been shown less effective than anticipated. Despite encouraging results in CRBSI prevention among adults, the goal of zero infection in children is still not in range. More high-quality research is needed in the field of prevention, accurate and reliable diagnostic measures and effective treatment of CRBSI in children.

Introduction

Central venous catheters (CVCs) are common and indispensable in modern pediatric medicine with an increasing number of patients requiring long-term vascular devices for various reasons. Common indications for CVC use are intensive care treatment with hemodynamic monitoring and infusion of vasoactive medication, hemodialysis as well as long-term use for chemotherapy, antibiotic treatment, parenteral nutrition (PEN) and replacement therapy for hematological or immunological diseases. CVCs provide secure vascular access, but they are also associated with catheter-related bloodstream infection (CRBSI) and central line-associated bloodstream infection (CLABSI), respectively. This review summarizes the recent literature about CRBSI and CLABSI in children focusing on long-term CVCs. The role of biofilm is discussed as well as measures for CRBSI prevention, diagnostic challenges in children, and the management of suspected infection.

Methodology

The literature search included PubMed with the search terms 'central venous catheter' and 'infection' with the limitation of age (children up to 18 years). Only articles published after 1999 and written in English were included. The title and abstract search focused on clinical studies, and only publications in line with all inclusion criteria were eligible for full-text review. Reference lists of reviews and clinical studies were used to retrieve additional literature from previous years. In total, 435 studies were retrieved for title and abstract sift in PubMed, and a total of 127 studies fulfilled the inclusion criteria for full-text review from which 95 studies were chosen for detailed qualitative assessment.

Results

CRBSI and CLABSI are multifactorial events with a reported incidence varying between 0.46 and 26.5 infections/1,000 catheter-days [1-4]. Infection rates vary with catheter types, indications, insertion sites, dwell times and patients' underlying disease. Implantable port systems have the most favorable risk, while infection rates are higher in tunneled catheters and nontunneled CVCs [5]. A number of risk factors for long-term catheters have been described such as PEN [3], young age

*Correspondence: arriba.a@gmail.com
[3]Department of Anesthesiology, Juliane Marie Center, Rigshospitalet, Copenhagen University Hospital, Blegadmsvej 9, 2100 København Ø, Denmark
Full list of author information is available at the end of the article

(<2 to 3 years) [4,6,7], low bodyweight (<8 kg) [8], increasing number of lumens in tunneled catheters [7] and hematopoietic stem cell transplantation [1].

The most common microorganisms include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, *Escherichia coli*, streptococci, enterococci, *Candida albicans*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [9,10].

Multimodal prevention strategies

Avoiding contamination that would lead to subsequent CVC colonization is supposed to be the key element in decreasing the risk of CLABSI [11]. CLABSI occurs through extraluminal contamination (microorganisms migrating from the insertion site along the external of the catheter) or intraluminal contamination (pathogens migrating from the catheter hub through the lumen of the catheter) with subsequent colonization and biofilm formation [12]. While extraluminal contamination is supposed to be the most common mechanism of CLABSI with short-term catheters [13], the intraluminal route is believed to be the more prevalent route of infection with long-term catheters (duration >10 days) [14].

A number of studies demonstrate the effectiveness of implementing standardized procedures and care bundles for CVC insertion and CVC care on CLABSI or CRBSI reduction. Elements for prevention upon CVC insertion include the use of maximum sterile barrier precautions, (alcohol-based) chlorhexidine for skin antisepsis, a checklist to stop non-emergent insertion and establishing fully equipped insertion carts [15-21]. Elements for prevention in CVC care include standardization of dressing change, skin antisepsis and replacement of tubing, and improving workflow at the patient [9,15-21]. Outcome reductions range from 70 to 83% using different strategies. No conclusion can be made for single interventions but only for the multimodal use of a defined set of procedures. Most studies applied a before-and-after study design and thus the quality of the studies is limited and the effectiveness in infection prevention may have been overestimated due to high baseline infection rates (7.8 to 8.6/1,000 days), but multimodal prevention strategies are still probably the most effective and important means of reducing CRBSI – especially for short-term catheters.

Biofilm formation in central venous catheters; prophylaxis and treatment aspects

Biofilm formation plays a major role in the pathophysiology of CRBSI. Biofilm acts both as a mechanical barrier and as an environment for genetic exchange and thereby contributes to protection from elimination by the innate host immune defense and to emerging antibiotic resistance. Biofilm formation is revealed to be a two-stepped process with initial adhesion of planktonic microorganisms and a subsequent maturation phase [22]. Bacterial expression of so-called microbial surface components recognizing adhesive matrix molecules has the capacity to bind to human matrix proteins such as fibrinogen or fibronectin [23]. Cofactors for the adhesion process are the presence of cations [24-26] and bacterial stress. The maturation phase of biofilm formation is characterized by intercellular aggregation and production of extracellular matrix leading to a typical three-dimensional structure. Bacterial lysis, DNA release and quorum-sensing systems play major roles in the development of the structure [27,28].

Most vascular devices develop biofilm within 24 hours after insertion [22]. The occurrence of CRBSI is proportional to the occurrence of microorganisms on the catheter tip, supporting the theory that a critical level of colonization is necessary for the detachment of planktonic bacteria, embolization and systemic infection [29,30]. The ability of a pathogen to form biofilm can be considered a virulence factor, as it is associated with mortality [31]. As metallic cations convey adherence of microorganisms to the surface of catheters, adhesion and thus biofilm formation is reduced by chelating agents [32-35]. *In vitro* studies found that ethylenediamine tetraacetic acid, citrate and *N*-acetyl-cysteine effectively reduce proliferation of *Staphylococcus epidermidis* and *C. albicans* and even eradicate existing biofilm [36].

Preventive lock solutions

Lock solutions in CRBSI prevention were tested almost exclusively in long-term CVCs. A recent study among adult hemodialysis patients found catheter lifespan prolongation using a lock solution with a highly concentrated chelating agent (sodium citrate 46.7%) in the absence of antimicrobials [37]. CRBSI was not reduced. Similarly, a lock solution combining citrate 7%, methylene blue and paraben effectively reduced infection rates in a recent study among adult hemodialysis patients [38].

Antibiotic CVC locks versus heparin locks were found effective in adults by a recent systematic review (relative risk = 0.37/catheter-day (95% confidence interval = 0.30 to 0.47)) [39]. Only one randomized controlled trial (RCT) has compared a vancomycine lock with heparin in a predominantly pediatric population, reporting a reduction of bacteremia among non-neutropenic patients [40]. Two RCTs evaluated the effect of adding vancomycine to PEN infusions in neonates and found bacteremia and CVC colonization significantly reduced [41,42]. *In vitro* studies suggested a synergistic effect by combining antibiotics, chelators and disinfectants [43-45]. A small proof-of-concept study confirmed the effectiveness of a lock solution combining minocycline and ethylenediamine tetraacetic acid on infection rates and prolonged

catheter survival as compared with heparin [46]. An additional small study reported a similar effect for minocycline/ethylenediamine tetraacetic acid among a small cohort of children with an implantable device [47]. There are no comparative studies between antibiotics alone and in combination with chelating agents.

Various non-antibiotic locking techniques have been proposed, such as taurolidine–citrate for hemodialysis catheters [48]. Taurolidine acts as a disinfectant, irreversibly damaging bacterial and fungal cell walls and disrupting biofilm, while citrate is a chelating agent [48]. Taurolidine–citrate locks reduced the incidence of bloodstream infection (BSI) due to Gram-negative organisms in two adult studies, but showed limited effect when BSI was caused by Gram-positive organisms [49,50]. In contrast, a recent study among pediatric hematology patients reported reduced overall BSI incidence in the taurolidine group as compared with the heparin group [51]. The study was very small, however, which puts the finding into perspective.

Ethanol locks, preferably at a concentration of 70%, have been studied mostly in children requiring PEN [52-54]. Ethanol appears to affect biofilm formation through protein denaturation [36]. A recent systematic review evaluated four studies among children treated by PEN and calculated a relative risk of 0.19 (95% confidence interval = 0.12 to 0.32) for CRBSI [52]. However, the included studies were heterogeneous, retrospective and small.

Impregnated catheters and dressings

In adults, technologies for infection prevention include catheters impregnated with chlorhexidine–silver sulfadiazine or antibiotics [55-58] and the use of chlorhexidine-impregnated dressings [59]. Availability of impregnated catheters for small children is limited and chlorhexidine-impregnated dressings were found to be causing contact dermatitis in neonates [60,61]. Furthermore, no studies have been done for children other than neonates.

Two systematic reviews about the use of impregnated catheters in adults found only significant and substantial reductions in CRBSI for heparin-coated and antibiotic-impregnated catheters, while no benefits were identified for antiseptic CVCs, coated with chlorhexidine and silver sulphadiazine, or silver-impregnated CVCs. [57,62]. The only RCT in children compared heparin-bonded against standard catheters [63]. Routine blood cultures were performed every 3 days and the catheters were cultured after removal. The hazard ratio for the endpoint of any positive culture result was 0.11 (95% confidence interval = 0.04 to 0.31) for children with heparin-bonded catheters.

Preventive strategies are summarized in Table 1.

Thrombosis and infection

The association between catheter infection and thrombosis has been suggested repeatedly although the results of the older studies were never really confirmed and the more recent publication is limited by size [64-66]. Although some authors argue that infection precedes thrombosis, a recent pediatric study suggested that thrombotic occlusion rather precedes infection [67]. Although fibrin deposition may provoke infection [68], the vast majority of hypercoagulability disorders do not seem to predispose for CRBSI [69].

A recent Cochrane systematic review of 12 RCTs comparing the preventive administration of anti-thrombotic agents (heparin or vitamin K antagonists) against placebo in 3,611 pediatric cancer patients only found a non-significant trend towards decreased incidence of symptomatic deep vein thrombosis and a nonsignificant reduction of CRBSI [70]. Another Cochrane systematic review identified two studies about preventive urokinase flushing versus heparin flushing, and no significant CRBSI reduction was identified [71]. One of the included studies reported fewer occlusive events in the urokinase group but no BSI reduction [72].

In summary, the interplay between occlusion, infection and deep vein thrombosis remains unclear. Although pathophysiologically such association appears likely, no formal association has been demonstrated in children, most probably due to the fact that both events are relatively rare.

Catheter-related bloodstream infection diagnosis

Confirming CRBSI in children is challenging. According to guidelines, blood cultures should be taken both from the central catheter and from a peripheral vein upon clinical symptoms, and CRBSI is most likely when the colony count from the catheter is fivefold to 10-fold higher than the colony count from the peripheral vein, or when the differential time to positivity between the two blood culture samples exceeds 2 hours [73]. Peripheral sampling is painful and unpleasant, and thus is not routine practice in children. Blood culture sampling in children uses smaller volumes (1 to 3 ml compared with 10 to 20 ml in adults), and although specially enriched culture media are used, the chance of isolating live organisms drops below 70% as compared with adults [74,75]. Correctly performed blood cultures are more likely to be positive [76]. Only two-thirds of the blood samples from infants <1 month old were adequate for culture, adequate being defined as containing an appropriate (age-related) volume of blood and being submitted in the correct blood culture bottle type. This information should prompt healthcare workers to be more careful when taking blood from neonates for blood culture [77]. If antibiotic treatment is initiated before sampling, the

Table 1. Strategies in the prevention of catheter-related bloodstream infections

Intervention	Method	Potential mechanism	Risk of harm	Population	Results	Comments	Level of evidence[a]
Care and management bundles [12,15-21]	Education Skin antisepsis Daily reassessment of indication	Preventing contamination	None	Patients in pediatric ICUs [15-18,21] Pediatric cardiac ICU [20]	Outcome reductions: 70 to 83%	No assessment of individual steps High baseline infection rates	2b
Impregnated dressing [59-61]	Chlorhexidine	Preventing contamination	Reported toxicity in children	Adults in ICUs [59] Neonates [60,61]	Hazard ratio = 0.402 (95% CI = 0.186 to 0.868) for CRBSI compared with conventional dressing	Only two pediatric studies (neonates) [60,61]	(1b)[b]
Antibiotic-impregnated catheters [58,60-62]	Minocycline / rifampicin	Preventing biofilm formation	Antibiotic resistance	All patients in RCTs requiring a CVC [58, 62] Adults requiring a CVC, >50% treated in ICUs [60]	RR = 0.26 to 0.39 for CRBSI compared with standard catheter	Unknown cost–benefit in children Limited availability for pediatric use	(1a)[b]
Non-antibiotic-impregnated catheters [58,60,62,63]	Heparin coating	Preventing biofilm formation	Resistance Anaphylaxis	Pediatric ICU [63]	Hazard ratio = 0.11 (95% CI = 0.04 to 0.31) compared with standard catheter	Unknown cost–benefit in children Limited availability for pediatric use	1b (1a)[b]
	Chlorhexidine–silver sulfadiazine coating			All patients in RCTs requiring a CVC [58,62] Adults requiring a CVC, >50% treated in ICUs [60]	Conflicting interpretations of results		–
Antibiotic lock [39,40]	Vancomycine; minocycline; gentamycine; cefotaxim	High antibiotic concentrations Penetrating and disrupting biofilm	Antibiotic resistance	Adults and children with end-stage renal disease undergoing hemodialysis [39]	RR = 0.37/day (95% CI = 0.30 to 0.47) compared with heparin (systematic review of all antibiotic locks; adult)	Long indwelling times may compromise feasibility Only one predominantly pediatric study with questionable choice of outcome	1b (1a)[b]
	Vancomycine			Patients with various malignancies and single lumen CVC, predominantly children [40]	Significantly reduced number of febrile and bacteremic episodes among non-neutropenic cancer patients		–
Non-antibiotic lock [37,51,52, 117,118]	Chelating agents	Protein denaturation Disruption of biofilm	Systemic adverse events Catheter damage	Adults with acute renal failure undergoing hemodialysis in ICUs [37]	Chelating agents: no significant results. Only adult studies	Long indwelling times may compromise feasibility	(1b)[b]
	Taurolidine–citrate			Children with various malignancies requiring a CVC [51]	Taurolidine–citrate: significantly reduced risk of CRBSI		1b
	Ethanol			Pediatric patients receiving PEN [52] Adult, hematologic patients [117,118]	Ethanol: no reduction in CRBSI		1b

CI, confidence interval; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; PEN, parenteral nutrition; RCT, randomized controlled trial; RR, relative risk. [a]Level of evidence refers to Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009 [http://www.cebm.net/index.aspx?o=1025]. [b]Level of evidence extrapolated from studies among adults.

sensitivity of the test is further reduced [78]. Incubation times often exceeding 72 hours and low sensitivity due to blood sampling make traditional blood cultures a lengthy process to rule out BSI [79,80].

As a consequence, new identification systems such as nucleic acid testing are promoted. Nucleic acid testing, which is based on pathogen lysis, nucleic acid extraction, purification, amplification and identification, can be used either to address a single pathogen of interest or to identify a large range of bacteria and fungi, even in a simultaneous process [81]. Techniques such as nucleic acid testing may serve to identify colonies isolated by culture or they may be applied directly to blood samples [81]. Protein-based identification via mass spectrometry by matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) is a rapid tool for pathogen identification, and is already widely established [82-84]. The technique uses mass spectral signals from clinical samples, which are compared with a reference database, thus allowing swift and accurate identification. MALDI-TOF has been shown to have limitations in the identification of some Gram-positive organisms or when the infection is polymicrobial [83]. However, prior culturing of organisms from clinical samples overcomes such limitation.

PCR-based diagnostics addressing housekeeping genes of microorganisms can theoretically be used directly in clinical material.

Quantitative detection of pathogen DNA without species identification may add information in confirming suspicion of CRBSI in children without prior culturing and can also detect bacterial DNA debris after initiation of antibiotic therapy [78,85]. In one recent study, there was a dose-dependent association between the amount of bacterial DNA per microliter of blood and suspicion of confirmed BSI [86]. Concentrations >0.5 pg/μl had a high positive predictive value for CRBSI.

The most intensively studied clinical method of simultaneous, pathogen-specific diagnosis is SeptiFast (Roche, Mannheim, Germany), a multipathogen probe-based real-time PCR system targeting DNA sequences of the bacterial and fungal genome simultaneously, which allows the detection of 25 common pathogens from one single blood sample [87]. The sensitivity/specificity values (60 to 95%/74 to 99%, depending on the pathogen) and positive predictive values of SeptiFast were superior to blood cultures in a number of studies, but the diagnostic value in clinical practice still awaits the results of large, well-designed clinical trials [81,88,89]. The test is rapid, but it identifies only a limited range of pathogens and does not provide information on antibiotic resistance, which is an important limitation in times of emerging resistance [87,89].

Management of catheter-related bloodstream infection

Suspected CRBSI creates the dilemma of whether or not to remove the CVC. Guidelines recommend this decision is made based on individual, clinical judgment [59,90]. The patient often still requires hemodynamic monitoring, fluid intake, PEN, and medication. CVC removal would therefore result in the insertion of a new catheter with the risk of mechanical and infectious complications and would expose the child to anesthesia. There is no RCT evaluating the evidence for early versus late CVC removal in neonates [91]. Only retrospective studies with conflicting conclusions are published [92-95].

CRBSI must always be treated with systemic antibiotics. However, while antibiotics are able to clear planktonic, free-floating microorganisms, their ability to eradicate biofilm-embedded organisms is limited due to low penetration into biofilm, changes in bacterial metabolism, antimicrobial resistance, and local alterations in the microenvironment of the biofilm that impair the activity of the antimicrobial agent [96]. To eradicate microorganisms embedded in biofilm, antibiotic concentrations would have to be 100-fold to 1,000-fold that required to kill free-floating organisms [97,98]. High antibiotic concentrations instilled in the catheter lumen for hours or days alongside systemic antibiotic therapy have been used with success rates between 31 and 100% depending on the pathogen [99-106]. Most studies reported treatment durations of 14 days. Four small pediatric studies about antibiotic locks reported immediate success rates ranging from 83 to 100%, but no information about long-term effects was provided [107-110]. While inclusion criteria and choice of antibiotic vary greatly in these studies, the vast majority of infections in all studies are caused by CoNS.

In summary, attempts at CVC salvage are only recommended in uncomplicated CRBSI or CLABSI caused by bacteria that are neither too virulent nor too difficult to eradicate – predominantly CoNS or enterococci [23].

Alternative strategies for CVC treatment include nonspecific disinfectants such as hydrochloric acid (HCl). HCl is thought to disrupt biofilm through denaturation of protein components in the extracellular matrix, exposing the microorganisms to subsequent antibiotic treatment [111]. The instillation of 2 M HCl was described in 2004 for the first time [112]. Three cycles of HCl exposure for 10 minutes within 1 day in combination with systemic antibiotic therapy that took into account the susceptibility of the identified pathogen resolved the infection in 28 out of 42 (67%) patients with persistent CVC-related bacteremia, defined as positive blood cultures >48 hours after the initiation of antibiotics. Another study of HCl instillation using a similar protocol was able to prolong CVC survival as compared with a historical control [111].

Although of concern, there are no data about catheter damage due to HCl treatment [113].

Ethanol also acts as a nonspecific substance interfering with the biofilm matrix and has a direct disruptive effect on microorganisms [114]. Attempted catheter salvage by ethanol locks with dwell times between 12 and 24 hours have been reported to be successful in 67 to 88% of published observational studies and case reports [114-116]. A small RCT identified a reduced CRBSI incidence using a 70% ethanol lock in tunneled central lines among hematology patients [117]. A recent large RCT failed to show any significant reduction in the incidence of endoluminal CRBSI, however, and thus its true benefit remains uncertain [118]. This uncertainty is further supported by preliminary results of another large RCT including 359 long-term tunneled or implanted CVCs, which failed to show any benefit of a 50% ethanol lock for CRBSI prevention [119].

Therapeutic strategies are summarized in Table 2.

Discussion

Avoiding contamination upon catheter insertion and catheter care is the cornerstone of CRBSI prevention, and a number of studies support the positive effect of improved routine procedures in the topic [9,15-21]. In pediatric settings, study designs are mostly quasi-experimental and neither high-quality studies nor robust analyses clearly document the effect of such interventions. This does not imply that best-practice procedures would not work, however, and it is most likely that they contribute notably to a reduced risk of infection. Documented declines in infection rates [21,120-122] allow the assumption that good clinical practice is pivotal in CRBSI prevention. These results are largely based on short-term CVCs in adult and pediatric or neonatal ICUs.

Although the contribution of the individual steps of what is called best practice is uncertain, multimodal intervention strategies were effective even if the combination of the specific interventions varied across the studies [123]. Bringing the risk of infection to the attention of healthcare providers already positively impacts patient outcomes. This phenomenon, called the Hawthorne effect, contributes to the positive outcome of many CRBSI prevention programs and thus should always be taken into account when interpreting data from quality improvement studies – especially in open-label protocols and when using a historical control group.

Although best-practice procedures of catheter insertion and catheter care to prevent bacterial colonization have been proven effective in CRBSI prevention, the principal pathogenesis of CRBSI is related to the catheter material itself promoting colonization with microorganisms and the formation of biofilm. As eradicating biofilms is difficult, if not impossible, preventing attachment and limiting biofilm formation are crucial tasks alongside correct catheter care in achieving the goal of zero infection – especially with long-term indwelling devices.

Maintaining best practice may be challenging with long-term CVCs and thus prophylactic locks have been intensively studied in pediatric patients using both antibiotics [40-42] and other antimicrobial substances [52-55] attempting to prevent the formation of biofilm. Despite evidence supporting antibiotics in lock solutions [39], there has been some reluctance to recommend such locks in routine use due to growing emergence of multidrug-resistant microorganisms [41,42,46,47]. A recent systematic review of 16 studies with a total of 176,332 CVC-days reported only one single case of bacterial resistance, but the authors argued that only few studies thoroughly addressed this issue and none performed surveillance cultures or examined long-term effects (>12 months) [39]. As for catheter salvage upon suspected BSI, pediatric studies are limited in quantity and quality. They provide limited evidence in favor of highly concentrated antibiotic lock solutions with long indwelling times, although the studies vary in design and choice of antibiotic [107-110]. On the other hand, the vast majority of detected and successfully treated CRBSIs were caused by CoNS and thus the findings are in line with the advisory guidelines, which propose that an antibiotic lock may be envisaged in uncomplicated CRBSI due to CoNS and enterococci [56]. It is of interest that primary outcome was either a subsequent negative blood culture or the absence of subsequent positive blood cultures. Bearing in mind the limited reliability of blood culture sampling in children, such an outcome may overestimate the treatment effect. A recent adult RCT failed to demonstrate a treatment effect because the calculated sample size was not achieved due to strict exclusion criteria [124]. Most frequently, patients were excluded because of permanent CVC use, which made an 8-hour to 12-hour lock impossible. This is frequently the case in children with CRBSI because the catheter may represent the only route of administration for fluids and nutrients, and the insertion of a temporary peripheral or central line may be technically difficult or undesirable due to anesthesia.

Prophylactic locks by non-antibiotic agents such as taurolidine–citrate [51], ethanol [52-54,117-119,125] and HCl [111,112] have been shown effective in pediatric settings. However, such locks imply a risk of inadvertent flushing or spillover to the systemic circulation. Due to low body weight this has more serious consequences in children, particularly in neonates. Taurolidine–citrate locks containing 4% sodium citrate provoked adverse events such as nausea, vomiting, and abnormal taste sensations in 20% of the children, possibly due to

Table 2. Treatment strategies for catheter-related bloodstream infections in children

Intervention	Method	Potential mechanism	Risk of harm	Population	Results	Comments	Level of evidence[a]
Catheter removal [92-95]	Physical removal	Eliminating suspected focus of infection	Insertion of new line may be required for adequate treatment	Neonatal ICU [92,93] Children with short bowel syndrome receiving PEN [94] Children with a CVC diagnosed with candidemia [95]	Conflicting interpretations of results	Individual, clinical evaluation recommended	2b
Systemic antibiotics	Conventional treatment of bloodstream infection	Killing susceptible free-floating planktonic micro-organisms	Depends on safety profile of each drug-	–	–	No pediatric studies of catheter colonization and biofilm disruption	–
Antibiotic locks [107-110]	Luminal instillation of highly concentrated antibiotic solutions for 8 to 12 hours daily for up to 14 days	Penetrating biofilm and eradicating susceptible embedded micro-organisms	Antibiotic resistance	Pediatric patients with confirmed CRBSI [107] Adults and children receiving PEN at home with confirmed bacteremia [108] Adults and children with chronic renal failure undergoing hemodialysis with confirmed CRBSI [109] Children receiving PEN with confirmed staphylococcal CRBSI [110]	Immediate success rates between 83 and 100%	Five small studies Questionable choice of outcome Treatment occupies the line for many hours	2b
Non-antibiotic locks [111,112, 114-116]	Ethanol: luminal instillation for 12 to 24 hours	Disrupting biofilm through protein denaturation and baring micro-organisms to systemic antibiotics	Systemic side effects	Children in pediatric ICU with confirmed CLABSI [114] Pediatric oncology patients with a CVC and bacteremia [115] Pediatric patients with a CVC and persistent bacteremia (>48 hours) [116]	Ethanol: immediate success rates between 67 and 88%	Ethanol: in large trials, benefit uncertain as a preventive measure	2b
	Hydrochloric acid: luminal instillation for 3×10 minutes within 1 day		Systemic side effects Possible catheter damage	Pediatric oncology patients with a CVC and bacteremia [111,112]	Hydrochloric acid: immediate success rate = 67% (85% CI = 52.9 to 82.3%) [112] Significantly more CVCs ***in situ*** after >100 days [111]	Hydrochloric acid: very few, small studies	2b

CI, confidence interval; CLABSI, central line associated blood stream infection; CRBSI, catheter-related blood stream infection; CVC, central venous catheter; PEN, parenteral nutrition. [a]Level of evidence refers to Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009 [http://www.cebm.net/index.aspx?o=1025].

spillover of citrate causing a drop in plasma concentrations of calcium and magnesium [51]. Possible adverse events at high concentrations such as 46.7%, as used in a successful trial [37], may include severe or even fatal arrhythmias due to electrolyte disturbances [126]. The side effects of ethanol are dose dependent and include dizziness, lightheadedness, tiredness, headache and liver toxicity [115]. In addition, disseminated intravascular coagulation and thrombosis have been reported as possible adverse events in children [53,54]. Ethanol locks, like antibiotic locks, require long indwelling times and thus their use is limited given the short time potentially available for locking in children often having only a single catheter. Spillover of HCl may cause hemolysis [112]. Such complications have not yet been reported, but generally the possible risks of HCl remain insufficiently investigated.

Antimicrobial coating of CVCs is another means to prevent infection, and impregnations with antibiotics or heparin have been shown of benefit [55,62,63]. However, most studies are unblinded and only one study has been performed in children. The study compared heparin coating with nonimpregnated catheters, and although CRBSI data had been obtained the reported outcome was all-cause BSI, which weakens the findings [63]. Most studies looked at catheter colonization as a primary outcome, which is questionable since a catheter may contaminate on removal. In addition, impregnated catheter tips can leak antimicrobials into the agar plate and thus provoke false negative culture results [62].

While there is evidence to support the use of antibiotic locks for CRBSI prevention, data for non-antibiotic locks in children are absent and well-designed studies are necessary to address this issue.

Quick and accurate microbiological diagnosis upon suspected CRBSI is of pivotal importance in pediatric critical care, but is challenging. New molecular techniques are promising, but not without shortcomings [81]. Methods such as MALDI-TOF are primarily add-ons requiring prior cultivation and although they shorten the time of pathogen identification, they do not overcome the challenge of low sensitivity of blood cultures in children due to inconsistent blood sampling [83].

Rapid multiplex real-time PCR tests to be applied directly to clinical samples may reduce the time to diagnosis [81]. However, existing PCR-based methods have not overcome shortcomings such as limited spectra of identifiable pathogens, limited antibiotic resistance testing, central laboratory facility requirements, lack of 24-hour availability and cost issues [87,88]. For the time being, PCR-based methods still require conventional culture being performed because susceptibility testing is paramount in today's emerging resistance. Ideally, PCR-based methods would be performed for rapid diagnosis of a pathogen, and blood cultures would be taken to confirm pathogen identification and to obtain antibiotic susceptibility. However, in pediatric and neonatal care settings, an additional sampling volume (for example, +1.5 ml for SeptiFast) may not be feasible due to practical limitations.

Strengths and limitations

While attempting to provide a broad review of the microbiological and clinical challenges with CVCs in children, long-term catheters appear to be over-represented compared with short-term CVCs, peripherally inserted central catheters and umbilical catheters. This imbalance is partially due to the fact that short-term catheters or CVCs in the neonatal ICUs are addressed often in best-practice multimodal improvement strategies while technical prevention methods were more probably applied to long-term catheters.

Some discussed results are based on various adult populations [37,39,55,57,59,62]. Catheters used for adults are of different length, diameter and material than those used for children, and there is a considerable difference in the disease spectrum indicating CVC placement and use in children and adults. There are also age-related physiological differences, which may affect the risk of infections related to the devices, especially the immaturity of the immune system and therefore relative immune incompetence in children.

Finally, children may have their CVCs longer than adults due to different clinical treatment regimes (that is, conversion from central to peripheral administration of medicine with increasing age) or merely due to the fact that critically ill children have better survival rates compared with adults.

Keeping in mind all of the above allows few overall evidence-based conclusions, and as such this review may leave the impression that little has been achieved. This is not the case, however, as multiple promising strategies have been proposed and indicate possible directions for future research.

Conclusion

Despite increasing research activity in CRBSI prevention in the past years, the goal of zero infection is still not in range – not for adults, and even less so for children. Insertion and care bundles addressing behavior change are difficult to implement in many hospital settings, and technology such as locks and antimicrobial impregnation of catheters are less effective than anticipated and many of them were tested in small studies of limited quality and rarely in children. For the time being, physicians must live with the limitations of blood sampling in children upon suspicion of CRBSI. New molecular tests, although promising, must show their effectiveness and

reliability in clinical practice. In general, more high-quality research is needed in the field of infection prevention in children. This does not only apply for CRBSI prevention, but is indeed true for the entire field of infection control.

Abbreviations

BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; CoNS, coagulase-negative staphylococci; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; HCl, hydrochloric acid; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; PCR, polymerase chain reaction; PEN, parenteral nutrition; RCT, randomized controlled trial.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Anesthesiology, Bispebjerg Hospital, Copenhagen University Hospital, Bispebjerg Bakke 23, 2400 København NV, Denmark. [2]Infection Control Program, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland. [3]Department of Anesthesiology, Juliane Marie Center, Rigshospitalet, Copenhagen University Hospital, Blegadmsvej 9, 2100 København Ø, Denmark. [4]Department of Pediatric and Neonatal Intensive Care, Geneva University Hospitals, Rue Willy-Donzé 6, 1211 Genève 14, Switzerland.

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