Prevention of catheter-related bacteremia in children on hemodialysis: time for action

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Abstract This editorial commentary discusses the strategies for prevention of catheter-related bacteremia (CRB) in children on hemodialysis, which is associated with high morbidity and the increase of hospital cost. There is evidence that the use of arteriovenous fistulae in children on hemodialysis is associated with lower infection rates. Therefore, the use of catheters in these patients should be decreased by improving arteriovenous fistulae use rates or by increasing peritoneal dialysis patient recruitment. However, despite the wide adoption of such policies, hemodialysis catheters are still being used in a significant number of cases. For these patients, implementation of effective strategies for preventing contamination of the catheter hub should be a priority. The appropriate recording and evaluation of CRB rates are important for assessing preventive policies. In addition, the successful management of a CRB is essential for preventing recurrence of bacteremia. Recently it was documented in a number of randomized clinical trials that antimicrobial lock solutions were effective for preventing CRB. It is suggested that the use of antimicrobial locks should be considered in children who are at high risk of developing CRB, with caution for their long-term use, because of the possibility of bacterial resistance. Now is the time for action, and all preventive steps should be performed simultaneously to minimize the risk of CRB.

Keywords Hemodialysis · Children · Vascular access · Catheter-related bacteremia · Intraluminal antimicrobial lock

Introduction

Creation and preservation of an adequate vascular hemodialysis (HD) access is a critical issue for children with end-stage renal disease (ESRD). Although an arteriovenous fistula (AVF) is preferred for long-term hemodialysis (HD) [1], tunnelled cuffed catheters (TCC) are used more frequently [2]. Actually, TCCs are often the only form of HD access in young children with relatively small vasculature, as the construction of an AVF or placement of an arteriovenous graft (AVG) might be very difficult or even impossible. In addition, TCCs have advantages such as the relative ease of insertion, pain-free dialysis, and immediate use. Catheter-related bacteremia (CRB) has been a major complication of the use of TCCs since their introduction in the early 1980s [3]. CRBs are associated with complications that affect dialysis adequacy, patient quality of life, and the cost of health care. In this issue of *Pediatric Nephrology*, Onder et al. report the effectiveness of tissue plasminogen activator (TPA) and tobramycin (TPA/TB) for prophylaxis of CRB in high-risk children on chronic hemodialysis [4]. The results of this retrospective study are encouraging, as TPA/TB locks may effectively reduce the rate of CRB in these patients and prolong the usability of their TCC [4].

TCC in children compared with AVF/AVG have been associated with an almost five-fold increase in hospitalization as a result of infections [5]. The high TCC use in children is partially explained by the expected expeditious transplantation and technical problems of AVF/AVG placement. Fortunately, high transplantation rates and the increased use of peritoneal dialysis (PD) in many countries limits the need for long-term HD in a number of pediatric patients. However, a significant percentage of children still need HD for extended periods of time. This is especially

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true for children who develop peritoneal membrane failure or are at high risk of recurrent disease, or with patients who resume dialysis after a failed renal transplant and are highly sensitized, or in difficult social situations. These children are at high risk to develop CRB, as the duration of TCC use is one of the most important risk factors for bacteremia [6]. Therefore, for such patients it is crucial to prevent CRB and to preserve vascular sites for use later in life. This commentary highlights the issues that should be considered in order to establish the appropriate strategies for preventing CRBs.

Epidemiological facts

TCCs continue to be the most commonly used vascular access for chronic HD in the pediatric age group, with a usage of 77% compared with 11% AVFs and 12% AVGs, as reported in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [7]. In addition, the cumulative incidence of infection-related hospitalization of pediatric dialysis patients was 40% in HD and 51% in PD [8]. The most important causes of bacteremia were vascular access for hemodialysis patients and peritoneal catheter for patients on PD.

It is encouraging that the incidence of intravascular-device-associated CRBs has decreased by nearly 40% during the past decade [9]. This was mainly the result of more consistent implementation of preventative measures. However, the incidence of CRBs still remains high and is a major cause of morbidity among children on HD. Although the true incidence of CRB associated with TCC is not known, an infection rate ranging from 1.6–5.5 episodes/1,000 days has been reported in most studies [10–12]. This broad range may reflect the variations in practice patterns. Undoubtedly, there are many centers not measuring this rate, accepting CRB as an unpreventable complication. Obviously, appropriate documentation of CRBs and surveillance of bacteremia are critical to infection control in dialysis units and improving quality of care [13]. A Centers for Disease Control and Prevention (CDC) survey of self-reporting US dialysis centers revealed a mean CRB rate of 1.5/1,000 days [14]. Therefore, rates above 2/1,000 days suggest problems with CRB prevention [15].

Pathogenesis of catheter-related bacteremia

The pathogenesis of CRBs is complex. Both bacterial pathogenicity and biofilm formation play a key role. However, other factors—including catheter surface characteristics, thrombosis, and immunological response—are equally important. For a microorganism to cause CRB, it

must first gain access to the extraluminal or intraluminal surface of the TCCs by one of two primary routes, depending on the length of time following the procedure of the catheter placement. Within the first month after TCC placement, catheters are colonized by the external route from the percutaneous tract mainly by organisms from the patient's skin and the hands of the medical personnel [16]. This is very rare in patients whose TCC was appropriately inserted in the operation room. Evidence-based insertion practices that use maximal barrier protection, topical chlorhexidine for skin disinfection before catheter insertion, and postinsertion skin disinfection procedures should be used in all patients to prevent catheter contamination. After the first month, TCCs are usually infected by the internal routes from contamination of the catheter hub, especially when TCC is inserted over a percutaneous guidewire or when it is later manipulated. This is the predominant mode of invasion of TCCs, and appropriate strategies for its preventions should be applied [16]. More rarely, hematogenous contamination of the catheter may occur from remote sources of local infection, such as pneumonia or, more commonly, a new reinserted catheter in patients with inadequately treated CRB might be contaminated hematogenously [17].

The polymer material of TCCs and its minute surface irregularities seem to activate an inflammatory cascade and have a thrombogenic effect [18]. Thrombosis is mainly responsible for the malfunction of TCCs and enhances the adherence and colonization of TCC with microorganisms. These pathogens are usually common environmental microorganisms including gram-positive, gram-negative and *Candida*. The invading microorganisms adhere to a multilayered complex structure referred to as biofilm [19].

The role of the biofilm

Electron micrographs of TCCs have revealed complex communities of different microorganisms covered by an extensive matrix, the biofilm [20]. Bacterial biofilms are responsible for the resistance to most antimicrobial treatments in a high number of patients with device-related and other chronic infections, such as otitis media, cholesteatoma, tonsillitis, cystic fibrosis, and prostatitis [21]. Biofilm formation in TCCs begins soon after TCC placement [16] and is the major source of CRB. The responsible bacteria for CRBs initially grow only in biofilms [22] and are recalcitrant to antibiotic therapy and insensitive to host defense mechanisms [23]. It is of interest that usually it is impossible to recover any bacteria from biofilms by traditional cultures. This leads to the misconception that bacteria are totally eradicated after the appropriate antibiotic treatment of a CRB.

Recently, with the application of modern molecular diagnostics, it was demonstrated unequivocally that bacteria are present in biofilms and are also metabolically active [21]. This might explain why a previous history of CRB remains the most important risk factor for bacteremia. In addition, the microorganisms isolated during CRB recurrence are usually different from those of the initial CRB. This is possibly the result of inadequate treatment of the polymicrobial biofilm, as once the dominant microorganism is eliminated by specific treatment, the suppressed colonies take over [24].

Microorganisms eventually migrate from the biofilm into the bloodstream with the potential to lodge in distant sites [20]. The majority of CRB episodes are relatively uncomplicated, but approximately 10% of patients with CRB are hospitalized with either severe sepsis (hemodynamic instability or high fever with shaking chills) or a metastatic infection such as endocarditis, osteomyelitis, septic arthritis, or epidural abscess [25]. These complications are 3.5 times more likely to occur when the infection is due to *Staphylococcus aureus* [26].

It has been recently documented that biofilms on the surfaces of TCCs may grow slowly, and the released circulating planktonic (free-floating) bacteria may be killed by normal defense mechanisms. Therefore, in such cases, the biofilms are essentially nonpathogenic but still responsible for causing inflammation and bacterial dissemination if they increase or if the host becomes compromised. Some factors may predispose dialysis patients to infection. The immunological system might be deficient in some patients with ESRD as a consequence of the accumulation of uremic toxins, neutrophil dysfunction, and hyperparathyroidism [27]. In addition, hypoalbuminemia increases the likelihood of a recurrence of bacteremia among patients treated for an initial CRB [28].

Biofilm is the source of chronic, subclinical inflammation due to the repeated stimulation of monocytes/macrophages. The release of proinflammatory cytokines may not only provide a strong stimulus for a sustained acute phase response, increased plasma levels of C-reactive protein, and erythropoietin resistance, but they may also favor activation of the coagulation pathways, leading to vascular access thrombosis [29]. However, at present, the extent and incidence of biofilm formation in HD patients have not been adequately investigated, as there are no methods to detect biofilm in vivo.

Time for agreement on diagnostic criteria of catheter-related bacteremia

CRB should be suspected when a child on HD develops fever or chills and there is no evidence for a source of

infection after the appropriate clinical and laboratory evaluation. A definitive diagnosis of CRB can only be made when blood cultures obtained from both the TCC and a peripheral vein grow the same organism. In addition, the Infectious Diseases Society of America has proposed that the colony count of the TCC blood culture should be more than five-fold greater than that of the peripheral vein [30], as a positive blood culture only from the TCC may simply represent colonization [25]. It was shown in oncology patients that a positive blood culture drawn through an indwelling central venous catheter with no confirmation from a culture from a peripheral vein had low positive predictive value. Therefore, a positive result from a catheter needs clinical interpretation and may require confirmation [31], and the diagnosis of CRB in a patient with a positive blood culture only from the TCC should be considered as probable and not definite [25]. However, using the most rigorous definition, it is possible to miss some cases of true CRB. In clinical practice, it is essential to start intravenous antibiotics immediately after obtaining the appropriate blood cultures in children on HD who develop fever or chills with no evidence for a source of infection.

Time for preventing recurrence of catheter-related bacteremia

The empiric therapy of CRB should include a glycopeptide antibiotic (vancomycin or teicoplanin) for a possible methicillin-resistant *Staphylococcus* infection and an aminoglycoside or a broad-spectrum cephalosporin for gram-negative bacteria. Obviously, the treatment should be modified when the pathogen has been identified and sensitivities are available. In addition, it is considered imperative to obtain blood cultures 1 week after completing the antibiotic regimen to document that CRB has been resolved [25]. However, it has been long recognized that treating CRB with systemic antibiotics alone, without catheter removal, is usually ineffective, as almost two thirds of these patients have a recurrence of CRB soon after discontinuation of antibiotics [32, 33]. Therefore, TCC should be removed with simultaneous insertion of a temporary dialysis catheter and then after a few days, a new TCC should be inserted. Although this approach is effective, it has the disadvantage of multiple procedures and the potential risk of central vein thrombosis, which may preclude future placement of a new dialysis catheter at that site [34].

An alternative strategy is to proceed to catheter removal only in the small percentage of patients (10–15%) with persistence of fever after 2 or 3 days of the initiation of therapy with the appropriate antibiotics. For the majority of patients, children with resolution of their fever, it is recommended to have their catheter exchange over a

guidewire (CEG). This approach was reported to be effective in adult HD patients [33, 35]. CEG offers the advantage of vascular access site preservation, which is very important, especially for children on long-term HD. Onder et al. recently reported that the overall and infection-free survival times of CEG versus removal and replacement of TTCs are comparable in children on HD with CRB [36]. However, the patients of this study were not randomly allocated, and there was a bias, with the sicker patients having their catheters removed and replaced.

More than 20 years ago, a new method for treating CRB in patients who received total parenteral nutrition [37] was first reported. This technique involves instilling a highly concentrated antimicrobial–anticoagulant solution at the end of a dialysis session which “locks” the catheter when it is not in use [38]. Although antibiotics can kill circulating planktonic microorganisms and treat CRBs, they cannot kill the biofilm pathogens that constitute the source of recurrent infections. Therefore, all efforts should be made to prevent biofilm formation [21]. The purpose of utilizing an intraluminal antimicrobial lock solution (AML) is to either prevent seeding or promote eradication of the microorganisms that colonize the catheter. The antimicrobial concentration used to eradicate microorganisms within the biofilm should be 100–1,000 times greater compared with the required concentrations to eliminate planktonic organisms. Such concentrations cannot usually be reached by systemic antibiotic therapy but might be achieved with the use of AMLs [38].

Capdevila et al. in 1993 first reported the successful treatment of 13 episodes of CRB in HD patients with an AML with heparin and vancomycin in conjunction with systemic antibiotics. None of the patients of these study required catheter removal to cure the CRB [39]. In two subsequent studies, with a vancomycin-gentamicin-heparin lock, 35% and 38% of patients, respectively, failed AML therapy and required catheter exchange [40, 41]. In a more recent prospective study, similar results were reported when gentamicin was replaced at the AML solutions with ceftazidime because of reported episodes of gentamicin-induced ototoxicity. The likelihood of a clinical cure was 87% for gram-negative infections, 75% for *S. epidermidis* infections, and only 40% for *S. aureus* infections [42]. In addition, all patients with CRBs caused by *Enterococcus* had a catheter exchange because in a previous study, a high incidence of secondary *Candida* infection in such patients treated with AML [43] was found. It was evident from this study that the overall success rate of implementing an antibiotic lock protocol for managing CRB in an individual dialysis program will depend on the relative frequencies of different bacterial pathogens.

Early AML application for optimal management of CRBs is essential. In a recent study by Onder et al., it

was reported that AMLs are significantly more effective in clearing CRB in children on HD when used early in infection, diminishing the need for catheter exchange [44]. An AML with tissue plasminogen activator (TPA, 1 mg/ml), tobramycin (5 mg/ml), and vancomycin (5 mg/ml) was used for 2 weeks following the initial empiric treatment of CRB in children on HD. CRBs were successfully cleared in 63/76 (83%) cases. The delay on the catheter exchange did not lead to metastatic infections or any other infectious complications [45].

Time for prophylaxis to prevent catheter-related bacteremia

Central venous access device contamination remains a persistent problem, even after more than 30 years of widespread clinical use. CRBs affect a number of patients requiring chemotherapy, antibiotic administration, or nutrition. However, the risk of contamination remains greater in HD patients because of frequent connections of the hub to dialysis lines, as colonization of TCCs usually occurs from the hub through their lumen. Therefore, the appropriate implementation of an appropriate technique for TCC handling is essential for reducing CRBs. Dialysis nurses have an important role in this standard TCC care. A significant reduction of CRBs by wrapping the catheter hubs with iodine-saturated gauze for 5 min before removing the catheter caps has been reported, having the dialysis nurse and patient wear masks during catheter connection and disconnection, and minimizing exposure of the catheter to air [11]. In addition, mandatory handwashing, clean gloves, masks, and use of nonocclusive dressings is recommended [46]. It is recommended that the exit site be cleansed with chlorhexidine 2% with 70% alcohol at each dialysis session prior to beginning the treatment. Another important recommendation from the CDC is that TCCs should not be used for any purpose but HD, including lab draws and IV therapy access, except in life-threatening emergencies [47]. Detailed recommendations for preventing CRBs were first published in 1973 [48] and are being updated frequently [49]. However, these recommendations are not universally applied [50]. Therefore, meticulous and continuous efforts should be made to provide appropriate training of dialysis personnel for the implementation of these preventive measures.

a. Preventing contamination of the exit site.

The subcutaneous cuff of TCCs promotes the local development of fibrous tissue, which serves as a mechanical barrier to bacterial invasion from the exit site. This is an important barrier, as it is well documented in two prospective studies that CRBs occurred two to three times

more frequently in HD patients with nontunneled catheters compared with those with TCCs [51, 52]. However, even in patients with TCCs, external route contamination from the percutaneous tract might occur, especially during the first weeks after their insertion. It has been recently documented in a randomized controlled trial that the risk of such infections can be reduced by topical thrice-weekly application of mupirocin ointment at the exit sites of TCCs. Mupirocin-treated patients experienced significantly fewer CRBs and a longer time to first bacteremia. It is also encouraging that mupirocin use was not associated with antimicrobial resistance [53]. Unfortunately, such resistance was described in other studies and might limit the effectiveness of long-term use of mupirocin [54]. In addition, all patients of this study had newly inserted TCCs, and there are doubts whether a similar effect could be documented in patients starting this management after long-term HD. Similar positive results were published by Lok et al. with the application of Polysporin ointment (bacitracin, gramicidin, and polymyxin B) or placebo at the exit site [55]. These studies indicate that the application of antibiotic ointments at the exit sites of TCCs might be significant for reducing *S. epidermidis*- and *S. aureus*-related CRBs, especially when it is used immediately after TCC insertion. However, long-term use of this regime has to be looked at with caution because of the possibility of antimicrobial resistance and the increase of infections caused by gram-negative bacteria.

b. Preventing contamination of the catheter hub

Despite the strict recommendations, contact of the catheter hub with the breath of the patient or dialysis personnel remains a major problem because of the high incidence of nasal colonization by *Staphylococcus*. It has been reported that nasal mupirocin application in such patients led to eradication of nasal *S. aureus* carriage in 96% of surveillance cultures and to a four-fold reduction in the incidence of *S. aureus* bacteremia during the 2 years period of the study compared with the historic control period. Once- or thrice-weekly maintenance regimens of mupirocin were equally efficacious. In addition, the incidence of bacteremia caused by other microorganisms was not significantly affected [56]. Unfortunately there is a relatively high recurrence rate of nasal colonization, and continuous treatment is necessary. Additionally, there is inadequate evidence for the effect of eliminating nasal colonization on the incidence of catheter infection [15]. The use of a mask by the nurse and the patient during TCC connection and disconnection and minimizing exposure of the catheter to air remain the most important interventions to prevent catheter-hub contamination [11].

c. Preventing CRB with the use of AML

The use of AML in newly inserted TCCs is designed to prevent biofilm formation. Instillation of high-concentration

heparin remains the most common method of “locking” a catheter since it was introduced in the early 1970s. There is evidence that heparin stimulates the growth of biofilm in vitro and higher concentrations of heparin increase biofilm faster than lower concentrations [57]. However, a major complication of heparin locks, especially in the perioperative period, is bleeding due to unsuspected anticoagulation [58]. This is the result of leakage of lock solution from the catheter due to parabolic flow patterns in the catheter [59, 60]. Trisodium citrate (30%) is an intraluminal locking agent that has been shown to significantly reduce the rate of CRB [61]. However, there is concern that this solution may cause significant hypocalcemia in the cases where higher amount of trisodium citrate accidentally enter systemic circulation. The US Food and Drug Administration (FDA) issued a warning regarding concentrated trisodium citrate after a fatal accident from a mistaken bolus injection of 46.7% citrate. The FDA also advised that a 4% citrate solution should be used as an alternative [62]. Recently, it has been shown that a 4% citrate solution is effective in maintaining catheter patency [63, 64] and has not been demonstrated to induce systemic anticoagulation or hypocalcemia. The same study found that the incidence of CRB before versus after switching from heparin to citrate 4% was similar.

Taurolidine, an antimicrobial agent effective against gram-negative and gram-positive bacteria as well as many types of fungi [65] has been used since the 1970s for a variety of wound types. Recently, it has been added to an AML with a 4% citrate solution [43]. Betjes and van Agteren evaluated the effect of this AML in patients with newly placed TCCs. Patients of the taurolidine–citrate group had a lower CRB rate compared with patients on heparin lock and had no increased requirement for thrombolytic interventions to maintain catheter patency [66], as was described by Allon [43]. Further studies, possibly with the addition of heparin to AML, might determine whether catheter patency can be improved. Unfortunately, there are no data on the use of this AML in children on HD.

A significant reduction of CRBs was also described with a gentamicin (40 mg/ml)–citrate lock in patients with newly placed TCCs compared with patients on heparin lock. Leakage of gentamicin from this AML was associated with dizziness, deafness, or ataxia in 7.5% of patients [67]. The risk of ototoxicity is a concern, especially in patients with long-term prophylactic aminoglycoside AML. There has also been one case reported of ototoxicity with the use of an amikacin AML [68]. A similar reduction of CRBs was reported with the use of a lower dose gentamicin (5 mg/ml) with citrate lock, and there was no evidence of systemic gentamicin exposure [69]. Therefore, the use of this lower gentamicin dose might prevent the development of ototoxicity.

Recently, 13 studies involving randomized clinical trials evaluated the rate of CRB in patients with AMLs with various antimicrobial agents versus standard heparin locks. AMLs with gentamicin with heparin [69–71] or citrate [67, 72] versus heparin were used in five of the 13 studies. In another two studies, AMLs with gentamicin with heparin were used; however, vancomycin [73] or cefazolin [74] was also added. In the eighth and ninth study, an AML of cefotaxime with heparin was used [75, 76]. The tenth study compared three different AMLs: gentamicin/citrate, minocycline/ethylenediaminetetraacetic acid (EDTA), and heparin [77]. The 11th study also compared minocycline/EDTA and heparin [78]. Finally, the last two studies compared AMLs of taurolidine/citrate 4% [43] and citrate 30% [61] with heparin locks. All these studies documented the effectiveness of AMLs.

Four studies involving meta-analyses of results from these 13 studies were published in 2008. Each meta-analysis evaluated seven to 11 clinical trials, five of which were common in the four studies. In all meta-analysis studies, a beneficial effect of AMLs was found. James et al. reported that the use of intraluminal antibiotics in 11 trials reduced the rate of catheter removal due to complication by 63% [79]. The meta-analysis of Labriola et al. of nine trials documented that the use of AMLs in TCCs reduced the incidence of CRB by about a factor of three [80]. However, the achieved incidence of CRB in the ALS groups is similar to published reports from units with low CRB incidence (and presumably stricter hygienic measures) [80]. Similarly, the meta-analysis of 11 studies by Yahav et al. showed that the treatment of four patients with AMLs prevented one CRB [81]. However the same meta-is does not support the role of catheter-lock solutions for patients with recurrent CRBs because the effect of AMLs was seen mainly in the first episode of CRB. The meta-analysis of the seven studies of Jaffer et al. found that the CRB rate with AML was 7.7 times less compared with heparin locks, and it was necessary to treat three patients with AML to prevent one CRB per 100 catheter days. In addition, CRB rates in heparin groups were similar in all seven studies (2.1–4.1/1,000 catheter days), and decreases in CRB achieved by using the different ALS were of similar magnitude [82].

The major problems of all trials are the use of cointerventions (i.e. application of antibiotic ointment at the exit site, use of nasal mupirocin) and the potential publication bias. Trials with negative results might not have been published; therefore, a possible selection bias could have occurred. It is encouraging that the recent meta-analysis studies do not provide evidence for the development of resistance with the use of AML [81]. Unfortunately, the limited follow-up of patients included in these studies does not exclude the onset of adverse events or bacterial

resistance with longer use of ALS [80]. Actually, there is some evidence that this possibility might occur. Monthly cultures of the bacteria colonizing the catheter lumen were obtained in a French dialysis unit routinely using gentamicin AMLs. After 2 years, 100% of the *S. epidermidis* isolates were resistant to most antibiotics [83]. The use of AML with taurolidine, trisodium citrate (30%), or EDTA might be of less concern, as bacterial resistance has not been reported to these agents. The possibility of bacterial resistance was the reason that the 2006 US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) vascular access guidelines did not include a recommendation for prophylactic antibiotics [49]. However, most studies documenting AML effectiveness were published after the development of these guidelines. In contrast, the CDC guidelines state that catheter-lock solutions can be considered only under special circumstances, such as multiple CRBs, despite maximal adherence to aseptic technique [47]. Finally, AML use should be considered in patients who are at high risk of developing CRB. This group of children includes patients with a history of recurrent infections or on immunosuppression, with a femoral TCC, a decreased serum albumin, or an elevated serum ferritin. In addition, AML use should be considered in children who are using one of their last potential dialysis access sites [84].

Conclusions

Catheter-related bacteremia in children in many hemodialysis centers remains a major concern because of the associated high morbidity and significant increase of hospital cost. Unfortunately, there is still a lack of documentation of the CRB rate in many centers. Appropriate CRB recording and surveillance should be a priority. A hemodialysis unit with a CRB rate above 2/1,000 days should focus on educating dialysis personnel in the use of appropriate sterile techniques [15].

Another important step for CRB prevention is to decrease the use of TCC, especially in children on long-term dialysis, who are at high risk to develop CRB. Successful AVF placement might be difficult or even impossible, especially in small children. However, numerous studies of successful AVF creation with microsurgical techniques in such patients have been reported. The recommendation of the K/DOQI guidelines for increasing the number of fistulas should be applied also in children. Early referral of children might be very important for enhancing “fistula-first” strategy. An alternative approach is to consider peritoneal dialysis or preemptive transplantation as first choice management in every child with ESRD.

Implementation of appropriate strategies for preventing contamination of the exit site and the catheter hub should

be a priority. Finally, there is enough evidence to support the prophylactic use of AML in a number of children with increased risk of developing CRB. Now is the time for action, and all the preventive steps should be performed simultaneously in order to minimize the risk of CRB.

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