REVIEW

Diagnosis and management of catheter-related bloodstream infections in patients on home parenteral nutrition

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ABSTRACT

Catheter-related bloodstream infections (CRBSIs) commonly arise from a parenteral nutrition catheter hub. A target for a Nutrition Support Team is to have a CRBSI rate of less than 1 per 1000. The diagnosis of CRBSI is suspected clinically by a temperature shortly after setting up a feed, general malaise or raised blood inflammatory markers. It is confirmed by qualitative and quantitative blood cultures from the catheter and peripherally. Treatment of inpatients may involve central venous catheter removal and antibiotics for patients needing short-term parenteral nutrition, but catheter salvage is generally recommended for patients needing long-term parenteral nutrition, where appropriate.

Significance of this study

- Catheter-related bloodstream infection (CRBSI) remains a very important complication for patients receiving home parenteral nutrition (HPN) and acts as a key quality indicator of their care.
- Studies have proven that CRBSI can be reduced and controlled in the HPN community by strict adherence to prevention measures, namely strict central venous catheter (CVC) care protocols.
- Tunnelled CVCs are considered to be the most desirable line of choice for their lower CRBSI and displacement rate, together with the easier ability for patients to self care.
- For centres with above-average CRBSI rates or for individual patients with recurrent CRBSIs, line lock therapy may improve rates.
- Paired central and peripheral blood cultures are required to diagnose CRBSI, using qualitative (differential time to positivity) and/or quantitative assessment.
- Efforts to be taken in order to prevent underdiagnosis or overdiagnosis of CRBSI as this can lead to inappropriate therapy include CVC removal.
- When clinically indicated, efforts should be made to salvage the CVC in order to prevent unnecessary CVC loss.

BACKGROUND

Central venous catheter (CVC)–related complications, particularly catheter-related blood stream infections (CRBSIs), are a major source of morbidity and occasionally mortality for patients with intestinal failure (IF) receiving parenteral nutrition (PN).[1–6] This applies to those receiving PN in both the hospital (types I and II IF) and home (type III IF) clinical settings. European Society of Clinical Nutrition and Metabolism (ESPEN) guidance for the management of chronic IF suggests that the incidence of CRBSI can be used as a quality indicator of care for the patient dependent on home PN (HPN)[7] and that patients with type II and III IF should be cared for in and by dedicated IF units.[7 8] A recent publication from the UK reported an extremely low inpatient CRBSI rate on a dedicated IFU over a 7-year period of 0.04 per 1000 catheter days, over a total of 23 548 inpatient catheter days.[9] For patients at home, CRBSI rates vary greatly between institutions both nationally and internationally, with reported rates between 0.22

and 11.5 episodes/1000 catheter days.[1 2 5–12] Variables that have been shown to influence CRBSI rates include education and training in CVC care,[11] experience of the MDT,[13] person responsible for primary CVC care,[11] duration of HPN, nature of underlying disease, patient age[14 15] intestinal anatomy and opiate dependency.[3 5 11 16–18]

PATHOPHYSIOLOGY

The infection most commonly arises from the hub of the indwelling catheter, but in some instances may arise from the infusate, if contaminated, or from haematogenous spread. Pathogens that do enter via the hub spread down the inner surface of the catheter, where they can form an adherent biofilm. With the passage of infusate through the catheter, the pathogen/s are transported into the circulation. This can be further complicated by the formation of catheter-associated thrombosis, which the pathogen/s can extend into causing infection of the thrombus.

PREVENTION OF CRBSIS

For centres delivering IF care, ESPEN stipulate CRBSI as a key quality indicator and so prevention of CRBSI occurrence, rather than treatment once they occur, is paramount to providing a high level of care. Adoption of such measures and strict adherence during ongoing care has been shown repeatedly to reduce CRBSI rate.

CVC type and site

Careful selection of the type and site of the CVC is paramount in reducing CRBSI rates. The number of lumens the device contains has been shown to influence CRBSI rates, with a meta-analysis of over 530 CVC insertions reporting a twofold risk of CRBSI events for devices with more than one lumen.[19] Moreover, management of an infected multilumen catheter can be complicated.[20] Tunnelled catheters are associated with a low rate of infection and are recommended by ESPEN as the CVC of choice for long-term HPN.[21] Implanted ports can be used, but patients may not like repeated skin puncture and, should they become infected, ports can be more difficult to salvage. Peripherally inserted central venous catheters (PICCs) can be the access of choice in certain scenarios, for example, tracheostomy, or when shorter-term PN is required, but in the HPN setting, PICCs are at increased risk of displacement. Furthermore, self-care of a PICC can be difficult due to the anatomical location and so may not be ideal for very long-term use[21] When upper venous access is not possible, femoral access is an option, but has been associated with increased incidence of CRBSI, again due to anatomical site.[22]

CVC care protocols

A dedicated CVC protocol is fundamental to CRBSI prevention, over and above any other prevention strategy.[23] A standardised approach needs to be communicated and adopted by patients, relatives and nurses caring for the CVC. The British Intestinal Failure Alliance (BIFA) has recently provided guidance aimed at standardising catheter care and, in doing so, has provided key principles for each element of CVC care in order to unify procedures between hospitals and reduce CRBSI rates; such key elements include the identification of 'key parts' required for PN administration and CVC handling and not touching them at any point during the procedure. Key parts include the catheter hub, the end of the giving set, syringe tip and the skin surrounding the exit site. Further standardised principles include handwashing, gathering and checking all equipment prior to commencing, the wearing of gloves and the use of 2% chlorhexidine gluconate.[24]

These standardised care protocols have been simplified wherever possible, in order to remove steps or elements that have not been shown to reduce CRBSI rates, such as the use of in-line filters.[7] Other non–evidence-based approaches, such as scheduled CVC replacement, should also be avoided. Hopefully, by standardising care, CRBSI rates will be reduced without a cost to the healthcare provider; indeed, dedicated and standardised care bundles have been shown to reduce CRBSI rates even in cohorts with already low rates.[25–27]

CVC care and training

Management of CVCs by highly trained nursing staff is key to maintaining low CRBSI rates,[3 7 28 29] and focused training of patients and carers to manage CVCs positively impacts on CRBSI rates.[3 17 30] Indeed, there is clear evidence that when CVC care is provided by dedicated highly trained nurses, the lowest CRBSI rates can be achieved.[9 11 31] An extremely low infection rate can be achieved when patients with type 2 and type 3 are cared for on a dedicated IFU.[9] While ESPEN and BIFA guidance advocate management of patients on such units, the target CRBSI rate that can be achieved needs consideration.[8] While a UK IFU has recently reported inpatient CRBSI rate of 0.04/1000 catheter days for new patients admitted to the unit over a 7-year period (over a total of 23 548 inpatient catheter days), it is apparent that the CRBSI rate can be much higher when patients are managed on general medical and surgical wards; for example, CRBSI rates of 5.1 per 1000 catheter days have been noted on medical-surgical ICUs, 5.8 per 1000 for trauma ICUs and 30.2 per 1000 for burn units.[32 33] In the general surgical and medical ward setting, CRBSI rates have also been shown to vary, with some studies reporting rates as high as 20.5 per 1000 catheter days.[34–36] Clearly, the type of line and clinical setting has a large impact on recorded CRBSI rates. However, it is equally apparent that institution of quality improvement techniques aimed at unifying insertion and subsequent CVC nursing care protocols can lead to significant

reductions of CRBSI rates on general wards. The role of dedicated nutrition nurses in preventing CRBSIs has been long established.[37] However, systems aimed at a systematic and coordinated approach to CVC care by all nurses handling CVCs for PN on any wards can improve outcomes throughout the hospital. Indeed, a recent study demonstrated a sustained reduction of CRBSI rates from 6.8 to 0.7 per 1000 catheter days on all general hospital wards outside of a dedicated IFU; this was achieved following the introduction of a nutrition support team that introduced measures including an intravenous access team to site dedicated and appropriate CVCs for PN, alongside training of all ward staff in aseptic procedures.[35] Thus, it may be reasonable for all nutrition support teams to set an inpatient CRBSI target of less than 1 per 1000 catheter days, by using quality improvement techniques to share best practice.

Given the need to preserve long-term venous access for patients with type 3 IF dependent on HPN, it is vital that CRBSI rates remain low after discharge from hospital. Traditionally, patient training for CVC care has occurred as an inpatient during their hospital stay prior to discharge, in keeping with available guidance. However, in more recent years, training has been intensified and modified, focusing on training patients and/or relatives in their own home and residential environments; notably, this approach has been shown to significantly reduce a patient's length of stay,[38] without having a detrimental impact on CRBSI rates.[11] There may be a role for novel training programmes, such as video education or dedicated residential training centres, which can positively impact of a patient's quality of life, as well as reducing the time spent by nurses to deliver the training required. However, the evidence for the impact of these novel approaches on CRBSI rates is either currently lacking or conflicting.[2 39]

Catheter lock solutions

There are a number of CVC lock solutions available, all of which involve the insertion and stasis of the solution in the lumen of the catheter while not in use (ie, between PN infusions aimed at CRBSI prevention).

Taurolidine

Taurolidine is derived from the amino acid taurine and has no reported toxicity for humans. Following its insertion to the CVC, it undergoes metabolic breakdown, the products of which interfere with microbial cell walls, which then prevents adherence of the microbes to the CVC lumen wall and potential biofilm formation. These effects can be seen with Gram-positive and Gram-negative bacteria, along with fungi.[40] Taurolidine has been shown to reduce the occurrence of CRBSI[40–43]; indeed, a recent study by Taurolidine has been shown to be able to decrease CRBSI risk by more than four times, compared with saline locks.[41] ESPEN has previously recommended the use of taurolidine for the prevention of CRBSI.[7] However, whether or not it should be used in all patients as primary prophylaxis, or in those with repeated CRBSIs, remains debated, not least because of the cost of its use in centres with existing very low CRBSI rates.

Ethanol

The reported efficacy of ethanol in reducing CRBSI rates across HPN and non-HPN cohorts is varied.[44–47] Ethanol CVC locks may have a role in CRBSI prevention for high-risk patients, for example, those with multiple CRBSI events, but this benefit does not appear to translate to the entire HPN population as[45–47] studies that have reported benefit frequently had above-average CRBSI rates prior to commencing ethanol locks.[48] John *et al* reported a reduction in CRBSI-related admissions from 10.1 to 2.9 per 1000 catheter days for patients receiving HPN.[49] Similarly, Jones *et al* saw the infection rate decrease from 9.9 per 1000 catheter days prior to initiation of ethanol locks to 2.1 per 1000 catheter days during therapy.[48] Both of these CRBSI rates are significantly greater than those reported desirable by international guidance and also from experienced IFUs.[1 7 9 11] A significant drawback to the use of ethanol locks relates to the risk of CVC thrombosis and occlusion.[50 51] Meckmongkol *et al* reported no reduction in CRBSI in their study cohort, but did report CVC-associated thrombosis rates increased from 0 to 3 per 1000 catheter days with ethanol lock therapy.[50] Moreover, there have also been reported concerns about systemic toxicity and the impact on the structural integrity of the CVC[52]; thus, ethanol locks are not currently recommended by ESPEN.[7]

DIAGNOSIS

The presentation of CRBSI can be atypical, but is usually suspected when there is fever and/or rigours within 30–60 min of commencing infusion.[53 54] The atypical modes of presentation can include raised bilirubin, hypoalbuminaemia and non-specific malaise, and patients can commonly have normal inflammatory markers.[53] These features can lead to missed opportunities to diagnose CRBSI or misdiagnosis.

The wide range in reported CRBSI rates between centres noted above[1 2 5–12] likely pertains to wide variation in patient cohorts included in studies, methods of CRBSI diagnosis and training protocols for CVC care. However, differences in catheter care protocols between centres are likely the most significant factor accounting for the extremes in CRBSI rates. That said, it is apparent that different diagnostic criteria are also applied in the identification of CRBSI. A number of international organisations have proposed diagnostic criteria for CRBSI, including the European Society of Clinical Nutrition and Metabolism and the Infectious Disease Society of America (IDSA).[21 54 55] A consensus opinion can be drawn from such guidance

Table 1 Most frequently reported pathogens leading to CRBSI and their reported frequencies[1 9 11 66]

Pathogen/s leading to CRBSI	Reported frequency
Coagulase-negative *Staphylococcus*	30%–50%
MSSA	4%–10%
Klebsiella spp	3.7%–12%
Other Gram-negative	5%–20%
Multiple organisms	10%–12%
Fungal	2.5%–11%

CRBI, catheter-related bloodstream infection; MSSA, methicillin-susceptible ***Staphylococcus aureus***.

defining CRBSI as "positive culture of the catheter (on removal), or paired blood cultures from a peripheral vein and the catheter (when left in place) with isolation of identical organisms (both species and antibiograms) from cultures of catheter segments and blood drawn from a peripheral vein in a patient with clinical symptoms of sepsis and the absence of another source of infection".[56] Furthermore, national and international guidance recommends the use of quantitative and/or qualitative microbiological analysis of the acquired blood sample/s. For quantitative analysis, pour plates are reported to have the best diagnostic accuracy.[54 57–59] When pour plates are used, a colony count of microbes cultured from the catheter hub blood sample at least threefold greater than the colony count from the peripheral blood should be used for the diagnosis of CRBSI.[54] When applying qualitative methods to the diagnosis of CRBSI, differential time to positivity (DTP) is widely available and provides a reasonable degree of accuracy. A positive CRBSI is diagnosed if the growth of microbes from the catheter hub blood sample occurs at least 2 hours before any microbial growth is detected in the peripheral blood sample.[60] Some of the most frequently reported pathogens leading to CRBSI can be seen in table 1.

Care needs to be taken when applying diagnostic criteria for CRBSI in order to prevent overdiagnosis and treatment, particularly since an inaccurate diagnosis can lead to unnecessary CVC removal and loss of venous access.[8] Therefore, all efforts should be made to maximise diagnostic yield and accuracy. Currently, there is no guidance that includes the consideration of 'probable' CRBSI, with this approach best avoided in order to prevent inappropriate therapy or line removal. Tribler *et al* demonstrated that a clinically based approach to diagnose CRBSI, that is, clinical features and positive cultures, rather than qualitative±quantitative analysis, may lead to significant overdiagnosis by 46%.[12] CVC tip culture is of limited clinical value given that salvage of infected CVCs is advised wherever possible.[21 61] Newer techniques for the diagnosis of CRBSI are emerging, but have yet to demonstrate benefit over existing methodologies. These include plasma immunoglobulin levels against flagellin and lipopolysaccharide and real-time PCR.[62–64]

BIFA have recently produced UK guidance aimed at standardising the diagnosis of CRBSI in adult patients receiving parental support.[56] Recommendations detail the use of quantitative or qualitative cultures as described above, noting that IF centres with no current access to DTP or pour plate methodology should work with their microbiology teams to introduce this service. All IF centres should then report annual inpatient and outpatient CRBSI rates/1000 catheter days, along with the associated method of diagnosis.[56]

MANAGEMENT

ESPEN guidance suggests that, once CRBSI is confirmed, CVC salvage should be attempted in order to prevent recurrent venous access change and potential risk of venous access loss.[8] There are, however, certain clinical situations where salvage should not be attempted and the CVC should be removed. These include septic shock, damaged CVC, poor CVC tip position, CVC tunnel infection, a metastatic infection (eg, endocarditis, osteomyelitis),[1 8 9 11 54] a bloodstream infection that continues despite antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *Staphylococcus aureus*, *Pseudomonas aeruginosa* or Mycobacteria.[54] Most international authorities would also recommend that CVCs infected with fungi be removed.[8 21 54 55 61] Despite the guidance relating to *S. aureus*, recent UK data have demonstrated that sustained salvage of *S. aureus*–associated CRBSI is possible in a high proportion of patients.[1 11] This ability to successfully salvage *S. aureus*–related CRBSI has also been supported by other studies from the USA[65] and Denmark.[66] When CVC salvage is clinically feasible and appropriate, 2 weeks of systemic antimicrobial (based on relevant sensitivities) in combination with CVC lock therapy should be used.[7] Two reports on the management of CRBSI have shown that this duration can be reduced to 10 days for coagulase-negative staphylococci while maintaining high salvage rates.[9 11] With that approach, salvage rates of 67%–72.5% have been obtained for all patients and as up to 81% for coagulase-negative staphylococcal CRBSI.[1 11 65] Some centres will use the CVC for parenteral support when salvage is in progress. There is no evidence in the literature to support this and is typically fluids or electrolytes only and after at least 72 hours of therapy with an appropriate clinical response.

For long-term catheters, particularly tunnelled catheters, the catheter hub is the major portal of entry for microbes causing bloodstream infection. Microorganisms that commonly cause CRBSI in patients receiving HPN are coagulase-negative staphylococci, Gram-negative bacilli, other Gram-positive bacteria (including *S. aureus*) and *Candida* species.[11] Around 10% of episodes are due to infections with multiple organisms. Antimicrobial therapy for CRBSI is usually

initiated on an empirical basis and subsequently modified when culture results become available. The initial choice of antibiotics will depend on the severity of the patient's clinical disease, the risk factors for infection and the likely pathogens associated with the specific intravascular device.[54] For the HPN population, it is important to cover for both Gram-positive bacteria (including coagulase-negative staphylococci) and Gram-negative bacteria empirically. It is therefore appropriate to consider a combination of intravenous agents initially, such as vancomycin (or daptomycin) for Gram-positive cover plus piperacillin–tazobactam (or a carbapenem or an extended-spectrum cephalosporin) for Gram-negative cover, depending on local susceptibility patterns. IDSA also recommend adding empirical cover for *Candida* species in patients receiving total PN,[54] although this is not routine practice in all IF units unless patients are critically ill.

Defining successful salvage has been debated with varying practice between IF centres internationally. For example, an IFU in the USA defined catheter salvage "as the process of treating an occurrence of CRBSI appropriately with antibiotics without removing the central venous catheter", while a UK IFU was more specific in defining salvage as "negative repeated sets of peripheral and central blood cultures and pour plates 48 hours after completion of antibiotic therapy".[1] This definition can be extended the definition as:

1. Resolution of clinical symptoms and signs of infection, plus
2. Negative blood cultures collected 48 hours post treatment, plus
3. No clinical or microbiological evidence of CRBSI with an indistinguishable micro-organism within 90 days of the end of treatment.

Using the UK definition has been shown to predict the absence of reinfection in 96% of patients over the following 1 year.[11]

RECURRENT INFECTIONS

If recurrent CRBSI is confirmed, then distant sites of infection should be considered, for example, discitis, lung emboli, urinary tract infection and endocarditis. Additional investigations that may be required include echocardiogram, venogram, CT and spinal imaging, the selection of which can be guided by clinical symptoms and signs. It is vital that patient and/or relative catheter care technique is assessed in the instance of CRBSI, and in particular those with recurrent CRBSI. Considering replacing self-care with nurse-led CVC care could be considered as a measure to reduce CRBSI rates,[11] and other measures that could also be considered include line lock therapies, for example, taurolidine.

CONCLUSION

CVC placement and ongoing management of the device is an integral part of treatment with HPN. With such placement comes the inherent risk of CRBSI, which can infer significant morbidity and mortality, including loss of intravenous access. The occurrence of CRBSI can also have significant financial implications with prolonged antibiotic treatment, recurrent hospitalisation, associated complications and need for repeated intravenous access removal/insertion. As such, it is vital that clear and well-adopted care protocols are strictly adhered to by self-caring patients and dedicated nurses, in order to reduce the occurrence of CRBSI. Similarly, implementation of CRBSI diagnosis guidelines is essential to prevent CRBSI misdiagnosis and subsequent inappropriate antibiotic use, together with needless catheter removal. A nationally or internationally agreed policy allows for a standardised CVC care as well as a uniform approach to CRBSI definition and management. Once a true CRBSI diagnosis is made, an attempt for catheter salvage is recommended for long-term catheters whenever safe, in order to prevent unnecessary removal and reinsertion of CVCs, which in the long term may lead to loss venous access, the latter being an indication for small bowel transplant.

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