# Catheter-related infections in patients with haematological malignancies: novel preventive and therapeutic strategies

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**Central venous catheters are essential for the treatment of patients with haematological malignancies and the recipients of stem-cell transplant. This patient population is, however, at high risk for catheter-related bloodstream infections that can result in substantial morbidity, mortality, and health-care-associated costs. Efficient prevention, early diagnosis, and effective treatment are essential to providing the best care to these patients. Although confirming the catheter as a source of infection remains challenging, the Infectious Diseases Society of America definition of catheter-related bloodstream infection remains the most precise definition to use in these patients. Gram-positive bacteria, particularly coagulase-negative *Staphylococcus* spp, remain the leading cause of catheter-related bloodstream infection, although an increase in Gram-negative bacteria as the causative agent has been noted. Although removal of the line and appropriate intravenous antibiotics remain the mainstay of treatment in most cases, novel technologies, including exchange with antibiotic-coated catheters and treatment with lock solutions, are particularly relevant in this patient population. In this Review we present the types of central venous catheters used in this patient population and analyse the different definitions of catheter-related infections, with an overview of their prevention and management.**

## Background

In patients with haematological malignancies and in recipients of stem-cell transplants, central venous catheters (CVCs) are essential to secure central venous access for blood product transfusions, chemotherapy, antibiotics, fluids administration, stem-cell infusions, total parenteral nutrition, and blood draws.[1–4] The use of CVCs might, however, be complicated by bloodstream infections. Annually, more than 5 million long-term CVCs are inserted in patients with cancer in the USA, resulting in 200 000–400 000 episodes of central-line-associated bloodstream infections (CLABSIs).[5,6] Risk of infection depends on host factors, as well as catheter type, and routine care procedures. Patients with haematological malignancies and stem-cell transplant recipients are at higher risk of infection than other patient populations, including other oncology patients, in view of their degree of immunosuppression and the wide use of blood product transfusions in this patient population.[7] Central-line infections in patients with cancer are associated with a reported mortality rate of 12–40%,[8,9] and they can result in delays in primary disease treatment, increased morbidity and mortality, prolongation of hospital stay, and substantial financial burden.[10–13] A 2013 report estimates the cost associated with one episode of CLABSI to be US$45 814, making CLABSI the most costly health-care-associated infection.[14]

In this Review, we present the types of catheters used in patients with haematological malignancy and in stem-cell transplant recipients, assess different definitions of catheter-related infections in this patient population, and present methods of prevention and treatment of such infections.

## Types of catheters used in patients with cancer

The most commonly used venous access devices in patients with cancer, including patients with haematological malignancies, include: peripherally inserted central catheters; percutaneous non-cuffed, non-tunnelled central venous catheters, such as CVCs, and cuffed tunnelled CVCs (including Broviac, Hickman, and Groshong); and subcutaneous port or reservoir.[4,12,15–17] In some institutions, tunnelled CVCs are increasingly being inserted by interventional radiologists as opposed to being surgically placed in the operating room, which makes their placement easier and less costly.[18] Peripherally inserted central catheters, ports, and tunnelled CVCs are currently the most commonly used catheters in patients with haematological malignancies and in stem-cell transplant recipients. Rates of infection vary depending on method[19] and timing[20] of catheter placement, and on catheter type. Several studies have suggested that implantable ports have lower risks of infection;[21–23] more recently it has been suggested that peripherally inserted central catheters have lower rates of infection compared with CVCs in the outpatient setting.[12]

## Defining catheter-related infection

Catheter-related infections include localised entrance-site or exit-site infections, tunnel infections and port-pocket infections, and catheter-associated bloodstream infections (catheter-related BSIs, or CRBSIs). Patients with cancer, particularly those with haematological malignancies and recipients of stem-cell transplants, are at increased risk of catheter-related infections;[11] however, the definition used for the National Healthcare Safety Network surveillance of central-line-associated bloodstream infection (CLABSI) currently lacks specificity in patients with cancer.[2,3] Although there is great variability in the definition of catheter-related or associated infection in the literature,[2] the two most commonly used definitions are the US Centers for Disease Control and Prevention (CDC) definition of CLABSI, and the Infectious Diseases Society of America (IDSA) definition of CRBSI (figure 1). CDC defines CLABSI as an isolated, laboratory-

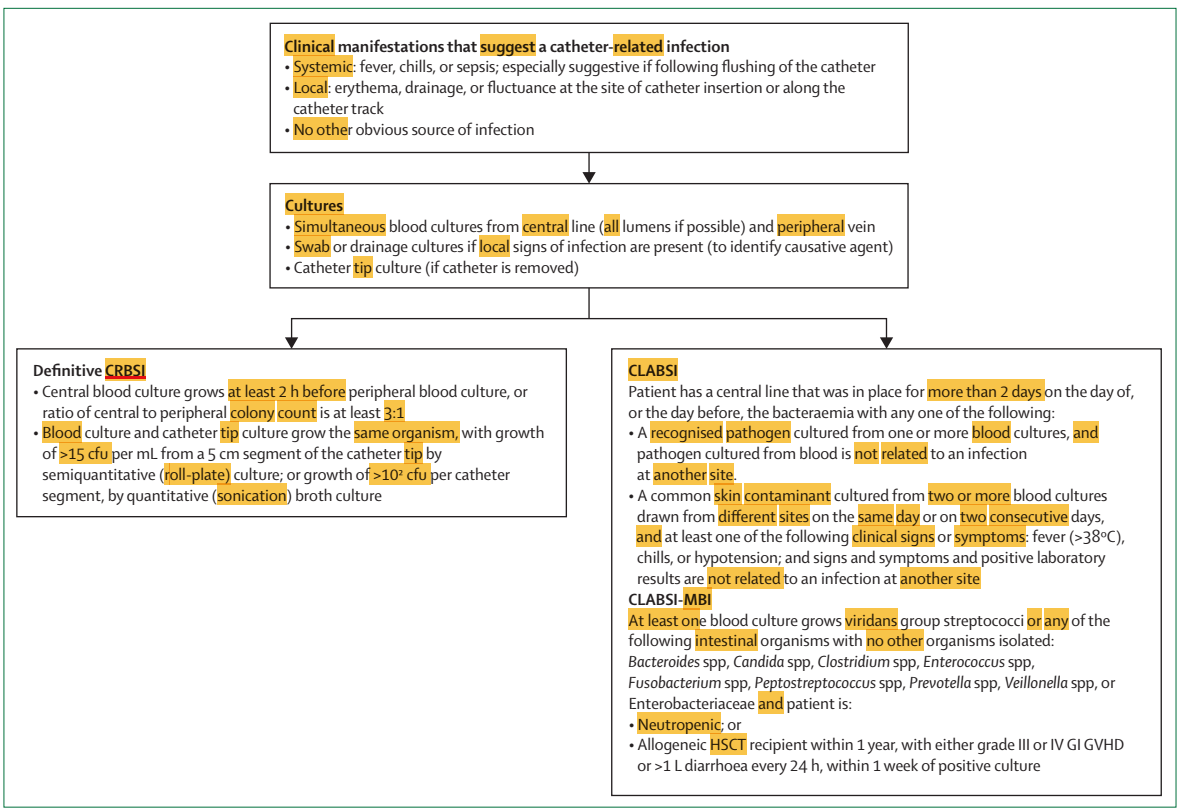


***Figure 1:*** **Flowchart for diagnosis of catheter-related bloodstream infection**
CRBSI=catheter-related bloodstream infection. CLABSI=central-line-associated bloodstream infection. MBI=mucosal barrier injury. HSCT=haemopoietic stem cell transplant. GI GVHD=gastrointestinal graft versus host disease.

confirmed primary bloodstream infection following a central line being in place for more than 2 calendar days. Criteria were recently introduced, in 2013, to the CDC definitions to identify patients with mucosal barrier injury who might have isolated bacteraemia, unrelated to the catheter but secondary to bacterial translocation.

According to IDSA guidelines, a definitive diagnosis of CRBSI requires: that the same organism grows from a peripheral blood culture and a culture of the catheter tip; that the same organism is detected at least 2 h earlier in a blood culture drawn from a catheter than a blood drawn from the peripheral site; or that the colony count of the same organism is three times greater from the central blood culture compared to the peripheral one.[8,16,24]

Applying the broad surveillance definition of CLABSI to patients with cancer, more specifically to those with haematological malignancies and recipients of stem-cell transplant, could result in an overestimation of the incidence of catheter-related infection, more so than in the general population. Neutropenia, mucosal barrier disruption, and changes in bacterial colonisation secondary to chemotherapy in patients with cancer can lead to isolated bloodstream infections, secondary to bacterial translocation in the absence of a catheter-related infection.[25,26] Results from a number of studies have shown that application of modified CLABSI definitions accounting for mucosal disruption in patients with cancer significantly reduces the number of reported CLABSIs in these patients.[25–27] This finding has driven the recent change to the CDC CLABSI definition accounting for mucosal barrier injury for specific organisms. Although this updated definition tries to limit overdiagnosis of CLABSI in immunocompromised patients, it has received several criticisms, including the requirement of data that might be hard to collect, the variability of implementation from institution to institution, and the exclusion of potential intestinal organisms that could be strongly associated with a catheter-related infection.[28,29] The CVC could still be the source of bacteraemia in a patient who might fulfil the criteria for a mucosal barrier injury. Results presented by our group in 2014 showed that 11 of 63 (17%) patients with CLABSI and mucosal barrier injury, as described by the CDC definition, meet criteria for a CRBSI.[30]

Although CRBSI, as defined by the IDSA, might require more specific laboratory testing, such as quantitative blood cultures, it is a more stringent definition that more thoroughly identifies the CVC as the source of the bacteraemia in patients with haematological malignancies and stem-cell transplant recipients.

Differential time to positivity of 2 h or more has been shown to be very sensitive and specific in patients with cancer, with short-term and long-term catheters,[31] and has been validated in stem-cell transplant recipients specifically as a marker of CRBSI.[32] On application of differential time to positivity to haematology patients with febrile neutropenia, 25 of 90 (27·7%) cases were found to be caused by CRBSI whereas all cases of bacteraemia would have been previously classified as CLABSI.[33] Results of a 2014 study similarly showed that CLABSI diagnosis provides an overestimate of the rates of catheter-related infections in patients with cancer: of 149 patients with cancer meeting CLABSI criteria, only 70 (47%) patients met CRBSI criteria.[30]

The management of catheter-related infections involves confirming the source of infection, making decisions related to the choice and duration of the systemic antibiotic therapy, and managing the central line by assessing whether it should be removed or if it could be retained. The management of the patient might depend on the severity of clinical presentation, the pathogen, the vascular access, and the presence of another source of infection. For some microorganisms, line removal is recommended in the IDSA's clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection,[16] particularly in the setting of severe sepsis and when no other source is identified. For less virulent microorganisms CVCs could be retained, particularly for patients requiring a long-term CVC to remain in place, to receive additional therapy, and in patients with limited vascular access sites. It is therefore important to make a definitive diagnosis of line infection to avoid unnecessary removal of the line. Definitive diagnosis is particularly important in the population of patients with haematological malignancies and stem-cell transplant recipients, who often present with thrombocytopenia, and in whom the insertion of a new CVC at a different site could potentially be associated with serious mechanical complications, such as pneumothorax and bleeding, and could frequently necessitate blood and platelet transfusions before CVC insertion. Duration of treatment can vary depending on whether the CVC was removed or retained. Management of the patient can also vary depending on whether there is another source of infection.

## Epidemiology of catheter-related infections

Patients with haematological malignancies have been shown to have higher incidence of catheter-related infections compared with patients with solid tumours. Within the population of patients with haematological malignancies, those patients with leukaemias have more catheter-related infections than those with other haematological malignancies, including lymphoma or myeloma.[21] Infectious complications related to CVC in patients with cancer occur at a frequency of 0·02–3·00 per 1000 catheter-days.[34] Studies reporting CRBSI in patients with haematological malignancies show a rate of up to 5·2 infections per 1000 catheter-days.[34] Bloodstream infections in patients with haematological malignancies are related to the catheter in 23·6–49% of cases,[11,34,35] with Gram-positive bacteria being the leading cause in 55% of bloodstream infections compared with 19% for Gram-negative organisms.[35] However, a 2015 study showed that with the turn of the century, there was a change in the microbial epidemiology of CRBSI in patients with cancer, with an increase in infections caused by Gram-negative bacteria and a decrease in those caused by Gram-positive organisms.[36]

Incidence of CRBSIs and the causative organisms can vary depending on catheter type. Results of a 2013 meta-analysis showed, in the inpatient setting, that peripherally inserted central catheters were associated with a CLABSI rate of 5·2% and other CVCs were associated with a CLABSI rate of 5·8%; in the outpatient setting, the incidence rates were 0·5% for periperally inserted central cathethers and 2·1% for other CVCs.[12] In patients undergoing autologous stem-cell transplant with a peripherally inserted central catheter in place, incidence of CRBSI was 3·3% (two of 60 patients) overall and 1·5 CRBSI per 1000 peripherally inserted central catheter-days.[1] Results of most studies identified in our search suggest an increased device-related infection rate in non-tunnelled CVCs compared with ports (2·77 *vs* 0·21 infections per 1000 device-days).[21] In patients with acute leukaemia undergoing induction chemotherapy, placement of peripherally inserted central catheters under ultrasound guidance and placement of Hickman catheters by interventional radiology, rather than by surgical placement, might be associated with fewer infectious complications (including exit site infection and bacteraemia). Gram-positive organisms are thought to be the organisms most commonly responsible for port infections (65·5%), whereas Gram-negative bacteria are possibly more commonly associated with other CVC infections (55%).[21]

The incidence of catheter-related infections, and the distribution of causative organisms in patients with haematological malignancies and stem-cell transplant recipients, also varies on the basis of the definition applied. When CLABSI definition and a modified CLABSI definition, taking into consideration intestinal bacterial translocation, were both applied in a population of stem-cell transplant recipients and patients with leukaemia, incidences of catheter-related infection per 1000 catheter-days were 6 and 2, respectively, for stem-cell transplant recipients and 14·4 and 8·12, respectively, for patients with leukaemia. When the modified CLABSI definition was applied, the most commonly involved organism was coagulase-negative staphylococci followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[27]

In a study looking at 110 episodes of bloodstream infections in 82 patients with haematological malignancy, the most commonly isolated organism in CVC-related bloodstream infection was coagulase-negative staphylococci, followed by

*Klebsiella* spp and *Candida* spp.[11] Results of other studies show that Gram-negative organisms are the most common organisms isolated in CLABSI.[25,26,37]

Cultures are polymicrobial in 9·8–36·0% of patients with haematological malignancies or following stem-cell transplant, who have catheter-related bacteraemia.[34,37,38] Mycobacteria and fungi (mainly *Candida* spp) have, respectively, been reported to account for 3.5% and 5·0% of CVC-related bloodstream infections in patients with cancer.[21]

## Risk factors of catheter-related bacteraemia

Although the results of some studies show thrombosis to be a risk factor for central-line infection, others show that there is no correlation between the two, or that bacteraemia might predispose a patient to thrombus formation.[39] Other risk factors that have been associated with CRBSI in patients with cancer are blood products and total parenteral nutrition administration,[7] as well as neutropenia status, with 65% of catheter-related infections occurring in patients who received a bone marrow transplant during the neutropenic phase.[40]

### Prevention of catheter-related infections

Microorganisms can penetrate the catheter through several routes. Migration of skin organisms at the insertion site, along the external surface of the catheter, is the most common method of contamination of short-term catheters (<10 days of dwell time—ie, time remaining in place), whereas direct contamination of the hub from contact with hands or other contaminated material is the most common method of contamination for long-term catheters that are often used in the treatment of haematological malignancies. Contaminated infusate and haematogenous seeding from other sources of infection may less commonly cause CLABSI.[17,41]

*Panel:* Preventive measures of catheter-related infections

**Education**

- Appropriate education of all health-care providers caring for a patient with a central venous catheter on the importance of catheter-related infection prevention
- Specialised teams: infusion therapy teams
- Simulation training

**Bundles**

- Hand hygiene
- Maximal barrier precautions: large sterile drape, gown, cap, mask, and gloves during insertion of central venous catheter
- Chlorhexidine skin antisepsis during insertion
- Optimal catheter site selection: subclavian preferred
- Routine assessment of central venous catheter necessity and prompt removal when not indicated
- Post-insertion care

**Antimicrobial catheters**

**Lock therapy**

Colonisation of the catheter and catheter-related infection could be prevented through several interventions (panel).

Although aseptic bundles should be applied and implemented during the insertion of short-term and long-term central venous access, they have been shown to decrease the risk of CLABSI with short-term CVCs.[42–45] Additional interventions, such as antibiotic-impregnated CVCs, antibiotic-coated CVCs, and lock therapy, are required to further decrease the risk of CLABSI associated with long-term CVC use.[42] Post-insertion care bundles that have been shown to decrease rates of infection[46] include: assessment of need for CVC, daily assessment of site of insertion, change of dressing at least weekly or whenever wet or soiled, use of chlorhexidine gluconate-impregnated sponge, applying alcohol scrub for 15 seconds before each access of the line, and hand hygiene. Continuous education and regular audits of bundle implementation might also be of benefit in lowering numbers of CRBSIs in oncology patients.[47]

The use of chlorhexidine gluconate-impregnated dressings was shown to decrease incidence of catheter-related infections by around 50% in patients with cancer, in one randomised, open, controlled study.[48] A Cochrane review suggests that chlorhexidine gluconate-impregnated dressings could reduce frequency of CRBSI compared with all other dressings; no substantial differences in terms of infection were noted between other kinds of dressings (gauze and tape, hydrocolloid, and highly adhesive transparent dressing).[49,50] It is unclear whether longer or shorter duration between dressing changes makes a difference in incidence of catheter infections.[51]

Topical application of antimicrobials at the site of catheter insertion, as well as systemic administration of antibiotics before catheter insertion, are not recommended for prevention and have not been shown to reduce the risk of infection.[50,52]

CVCs impregnated with minocycline and rifampicin have been shown to significantly decrease the risk of CRBSI in patients with cancer, with no evidence of an increase in resistance of the staphylococcus isolates to minocycline and rifampicin after long-term use of these devices.[53–56] However, the antimicrobial durability is only about 28–50 days.[54,57] Results of a 2016 Cochrane review of antimicrobial-impregnated catheters in different settings—in intensive care units, patients with cancer, and total parenteral nutrition—including 57 studies using 11 different impregnations, showed that use of these catheters decreased the number of CRBSIs.[58] Minocycline-rifampicin impregnation was superior to silver-platinum carbon and chlorhexidine silver-sulphadiazine impregnation in decreasing the number of CRBSIs.[58]

Ethanol locks have been studied as a means to prevent CVC infection, with variable results; recently, some safety

concerns regarding the 70% ethanol concentration have arisen.[59] Results from a randomised trial looking at adult patients with haematological malignancies, with Hickman lines, did not show any benefit in using 70% ethanol lock in preventing catheter-related infection.[60] Additionally, the use of 70% ethanol alone was associated with a significantly higher rate of adverse events than with the placebo.[61] However, a paediatric randomised controlled trial showed a decrease in the number of catheter-related infections in children with cancer with tunnelled CVC and the use of 70% ethanol locks.[62] Ethanol locks should be used with caution and at concentrations lower than 28%, as high concentrations of greater than 60% ethanol have been reported to cause mechanical damage to the integrity of the catheter polymer[55] and concentrations greater than 28% could cause plasma protein precipitation.[63] However, when ethanol locks are used alone, prolonged dwell time may be necessary to inhibit biofilm formation.[64]

Antimicrobial locks could play an additional part in the prevention of infection of CVCs that are projected to remain in place beyond 7 weeks. Flushing or locking the line with an antibiotic (vancomycin, vancomycin and amikacin, or taurolidine) and heparin combination might prevent Gram-positive catheter-related infection in patients with cancer at high risk of neutropenia by around 50%.[52] Lock solution containing minocycline and ethylenediaminetetraacetate (M-EDTA) has been shown to prevent port infections in children with cancer.[65] Furthermore, M-EDTA lock solution prevented the relapse of CLABSI in three patients who had experienced a total of 40 CLABSIs during a cumulative period of 76 months.[66] Similarly, M-EDTA lock solution was shown to prevent the recurrence of CLABSI in chronic haemodialysis patients.[67] A prospective, randomised trial involving 60 haemodialysis patients with long-term CVC showed that M-EDTA significantly decreased catheter colonisation compared with the heparin group, and substantially prolonged catheter survival.[68] Non-antibiotic lock solutions, such as nitroglycerine citrate lock, have also shown efficacy in eradicating organisms embedded in biofilm on catheter surfaces, and they may be helpful in preventing catheter colonisation and infection in clinical settings.[69] A 2014 meta-analysis suggested that antimicrobial lock solution should be considered as a preventive strategy to reduce the risk of CLABSI.[70]

Finally, technologies permitting very early and rapid

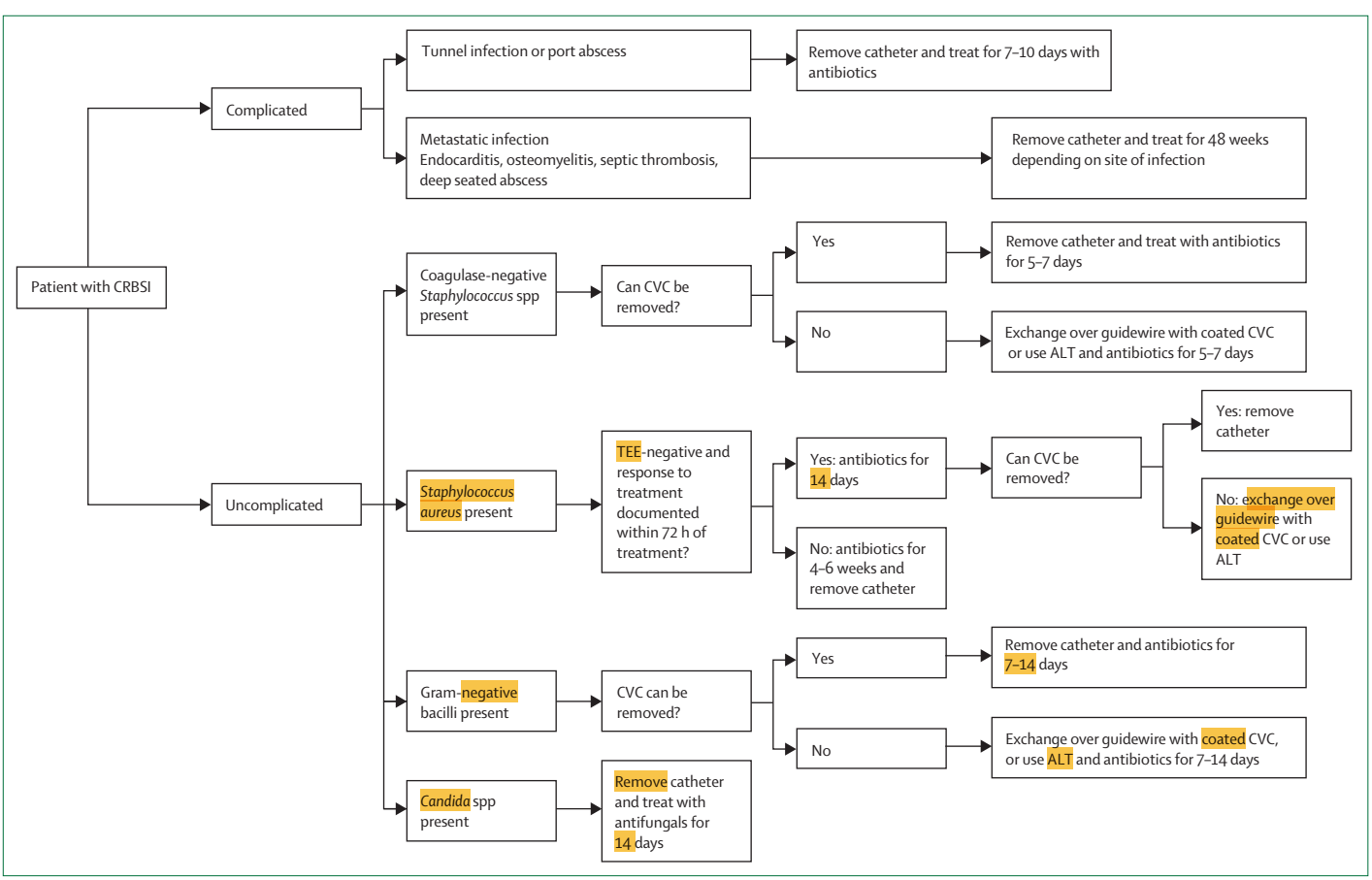


***Figure 2:*** Treatment algorithm
CRBSI=catheter-related bloodstream infection. cfu=colony-forming units. CVC=central venous catheter. ALT=antimicrobial lock therapy. TEE=transoesophageal echocardiogram.

detection of catheter infections, such as fluorescence in situ hybridisation with peptide nucleic acids, could help to prevent complications associated with later full-scale infection.[71]

## Treatment of catheter-related infections

### Catheter management

*Catheter removal*

In conjunction with targeted antimicrobial therapy, catheter removal remains the mainstay of treatment of catheter-related infections in the majority of cases (figure 2). In a report reviewing Hickman-line-related infections in non-neutropenic patients with haematological malignancies, 73% had to have their lines removed because of haemodynamic instability at presentation or persistence of fever and culture positivity. This proportion increased to 86% when considering only infections related to Gram-negative organisms.[37] However, the ability to remove the catheter relies on several factors including availability of other vascular access, and, in patients with haematological malignancies or stem-cell transplant recipients, adequate platelet counts and ability to achieve adequate haemostasis. Reports from patients with haematological malignancy or stem-cell recipients describe catheter removal rates in the setting of a CRBSI as low as 25%.[72] Retaining the catheter in the absence of other salvage measures aside from routine antibiotic administration could, however, result in high rates of failure of treatment, or recurrence of infection. In one report evaluating CRBSI in patients with haematological malignancies or stem-cell transplant recipients, patients in whom the catheter was not removed had significantly increased rates of failure of treatment—considered as recurrence of infection within 90 days or death within 30 days due to sepsis—as well as an increased rate of recurrence of bacteraemia with the same organism within a 90 day follow-up period, although there was no difference in mortality. 46% of patients who were managed without line removal had recurrence of infection; 72% of those were accounted for by coagulase-negative staphylococci and 28% by Gram-negative bacteria.[38] Failure of treatment and need to remove the line is organism-dependent. In patients with cancer who have *S aureus* bacteraemia, early removal of the catheter within 3 days of bacteraemia is associated with better outcome.[73] In 188 patients with cancer, including 134 patients with haematological malignancies or stem-cell transplant recipients who had coagulase-negative staphylococci catheter-related bloodstream infection, CVC retention did not affect the resolution of the bacteraemia, but it was associated with a 6·6-times increased risk for recurrence.[74] In a study evaluating Gram-negative CRBSI in 72 patients with cancer (most with solid tumours), catheter retention was associated with relapse of infection. Organisms associated with relapse of infection included *Enterobacter* spp, *Pseudomonas* spp, *Klebsiella* spp, *Stenotrophomonas* spp, *Acinetobacter* spp, *Serratia* spp, *Escherichia coli*, and *Proteus* spp. Prompt removal of the catheter in patients with cancer who have *Stenotrophomonas maltophilia* bacteraemia has been shown to result in better prognosis.[75] Recommendations are to remove the catheter within 48–72 h of documentation of a Gram-negative CRBSI whenever possible, on the basis of better outcome and decreased relapse rates.[8] Early catheter removal in catheter-related candidaemia (within 72 h of initial candidaemia) has a substantial effect on response to antifungal therapy.[76] Although findings of other studies have suggested that early removal of the catheter in patients with candidaemia may not be necessary, these studies included patients without cancer and reviewed candidaemia in the setting of a CVC in general, without distinguishing episodes judged to be truly related to the CVC from others.[77,78]

Although catheter removal is the conventional approach to catheter management in CRBSI, removing the CVC and replacing it in a different location may be challenging in patients with haematological malignancies or stem-cell transplant recipients. Furthermore, insertion of a new CVC at a different site could be associated with serious mechanical complications in this patient population, particularly in the setting of thrombocytopenia and coagulopathy. More novel approaches have been shown to be viable solutions in such cases, including exchange of the CVC over guidewire with a minocycline-rifampicin-coated catheter, or administration of antimicrobial lock therapy along with systemic antimicrobial therapy.

*Catheter exchange over guidewire using antibiotic-coated CVC*

Exchange over guidewire using an antimicrobial CVC should be considered as an alternative in patients with non-surgically implanted CVC who cannot have the CVC removed and replaced. Results from a matched retrospective cohort study of patients with cancer showed that, in the setting of CLABSI, exchanging the CVCs over guidewire with a minocycline-rifampicin-coated catheter in an attempt to salvage the vascular access may improve the overall response rate to systemic antimicrobial therapy and decrease the rate of recurrence, compared with removal of the CVC and insertion of a new CVC at a different site, while decreasing the rate of mechanical complications.[79] Similarly, results of a study using an in-vitro over guidewire exchange model that evaluated different antimicrobial CVCs, showed that catheters coated with minocycline-rifampicin-chlorhexidine were the only CVCs effective in completely preventing cross-contamination with multidrug resistant bacteria and candida during over the guidewire exchange procedure.[80,81]

*Antimicrobial lock therapy*

When removal of the line is not possible, particularly for ports and other surgically and non-surgically implanted

CVCs, antimicrobial lock therapy (ALT) in adjunction with systemic ALT is recommended (figure 2). Traditional lock therapy consists of the instillation of 2 mL of an antibiotic at 100–1000 times the usual systemic concentration, into the line. In a meta-analysis that reviewed studies comparing treatment with antibiotics combined with ALT to antibiotics alone, or combined with replacement of the line, the catheter had to be replaced in 10% of patients receiving lock versus 33% of patients without lock.[82]

Vancomycin, alone or in combination with heparin, has been the most commonly used ALT solution; however, it is associated with remarkable failure, especially in CLABSI caused by *S aureus*.[66,83–85] This might be related to the fact that glycopeptide antimicrobials, such as vancomycin, have a limited activity against organisms embedded in biofilm on a catheter surface.[86–88] The combination of 25% ethanol with M-EDTA lock solution has been shown to eradicate pathogens such as meticillin-resistant *S aureus* (MRSA), multidrug resistant Gram-negative bacilli, and *Candida parapsilosis* embedded in biofilms, and may be of clinical efficacy in salvaging catheters.[6,89,90] Combinations of ethanol with other antimicrobials are being investigated for salvage of infected catheters, including those infected with organisms such as *Stenotrophomonas* spp and MRSA.[89,91] A prospective pilot clinical study, using a lock solution containing M-EDTA in combination with 25% ethanol to salvage CVC in more than 40 episodes of CLABSI due to various organisms, showed promising results; the CVC was salvaged in all patients, with complete resolution of the bacteraemia and no relapse.[92] Patients receiving the lock had a significantly lower rate of mechanical and infectious complications, compared with patients who had CVC removal and reinsertion.[92]

Because of the limited number of patients enrolled, and the limited number of well designed prospective randomised studies in this patient population, large, prospective, multicentre randomised clinical trials evaluating the role of novel antimicrobial lock solutions, particularly in this patient population, are warranted.

### Systemic antimicrobial therapy

Duration of treatment varies depending on the organism isolated, the presence or absence of complications, and whether the catheter has been removed or not. Day one of treatment should be counted as the first day on which a negative blood culture is documented.[16]

Follow-up blood cultures should be used to document response to treatment, especially if the catheter is retained. If the patient has persistent positive blood cultures up to 72 h after initiation of appropriate therapy, the catheter should be removed.

### *Staphylococcus* spp

Vancomycin is still the gold standard of empirical treatment of Gram-positive CRBSI, pending culture results and susceptibilities, and for meticillin-resistant organisms; however, daptomycin has been shown to be at least equally efficacious as vancomycin in the treatment of Gram-positive CRBSI in patients with cancer and may be associated with faster symptom resolution and microbiological eradication as well as better overall outcome.[93] Daptomycin is thus a good alternative in patients with haematological malignancies who might be at increased risk of harbouring vancomycin-intermediate or vancomycin-resistant *S aureus*, or in patients who are at increased risk of vancomycin-associated nephrotoxicity, such as those receiving other nephrotoxic drugs.[94] Performing a transoesophageal echocardiogram on all patients with *S aureus* catheter-related bacteraemia is cost-effective, and could help limit the course of antibiotics in patients, with no other complications secondary to the staphylococcal bacteraemia (figure 2).[95] A recent study evaluating 304 episodes of *S aureus* CLABSI in 299 patients with cancer showed that the majority (67%) are considered to have complicated bacteraemia and require a prolonged course of antimicrobial treatment. Patients were considered to have complicated *S aureus* bacteraemia if they fulfilled any of the following criteria: retention of a foreign body, evidence of infective endocarditis or deep-seated infection, persistence of fever or bacteraemia after 72 hours of initiation of adequate therapy, recurrence of bacteraemia during the follow-up period (3 months), or infectious-related mortality. However, in the 33% of patients with uncomplicated bacteraemia, 14 days of treatment with antibiotics was sufficient.[73] Coagulase-negative staphylococci is typically thought to be of low virulence or, frequently, a contaminant. Coagulase-negative staphylococci CLABSI can be treated for a shorter duration of 5–7 days.

### Gram-negative organisms

The 2009 IDSA guidelines for the management of intravascular catheter-related infection recommend treating with systemic antibiotic for 7–14 days and removing the catheter.[16] Gram-negative empirical coverage should include a fourth-generation cephalosporin, carbapenem, or beta-lactam/beta-lactamase combination, with or without an aminoglycoside. Combination therapy should be used in patients with neutropenia, who are septic or have a history of multidrug-resistant Gram-negative organisms.[16]

### *Candida* spp

*Candida* spp account for 98% of catheter-related fungaemias in patients with cancer.[96] In a study evaluating 404 episodes of candidaemia in patients with cancer (49% with haematological malignancies), 111 were deemed related to the catheter, on the basis of catheter culture or quantitative blood cultures. *C albicans* and *C parapsilosis* were the two most frequently isolated *Candida* spp with catheter-related infections (44% and 23% respectively). All patients with candidaemia should

### Search strategy and selection criteria

We searched PubMed for articles relevant to epidemiology, diagnosis, prevention, and treatment of catheter-related infections in patients with cancer, haematological malignancies, or who have received a stem-cell transplant. We reviewed articles published between June 1, 1987, and March 31, 2016, that were retrieved using the following search terms: "central venous catheter", "infection", "cancer", "hematologic/haematological malignancies", and "stem cell transplant". Only papers published in English were reviewed.

receive antifungal therapy such as fluconazole. However, for *Candida* spp with decreased susceptibility to azoles (such as *Candida glabrata* and *Candida krusei*), echinocandins or lipid formulations of amphotericin B should be strongly considered. Patients already on azole prophylaxis should be started on echinocandins.[16]

### Other organisms

Some organisms that can otherwise be considered contaminants have been specifically shown to persist in the absence of removal of the catheter, including *Bacillus* spp[74] and *Micrococcus* spp,[97] and treatment of infection caused by these organisms in patients with cancer, along with early removal of catheters might be beneficial.

## Conclusion

Although removal of the line and appropriate intravenous antibiotics remain the mainstay of treatment in most CRBSI cases, novel classes of antimicrobials and novel technologies to target resistant pathogens embedded in biofilms are particularly relevant in this patient population.

**Contributors**

All authors provided feedback and guidance on the analysis and interpretation of the results, contributed to the drafting of the manuscript, critically reviewed the manuscript, and provided final approval for submission.

**Declaration of interests**

IIR is coinventor of technology related to minocycline and rifampicin-coated catheters. This technology is licensed to Cook, Bloomington, IN. IIR receives royalties related to this technology, which is owned by The University of Texas MD Anderson Cancer Center (UTMDACC). IIR is also a coinventor of the minocycline-EDTA-ethanol lock solution technology, which is owned by UTMDACC and has been licensed to Novel Anti-Infective Technologies, Houston, TX, LLC, which has sublicensed the technology to Leonard-Meron Biosciences, Cranford, NJ, of which UTMDACC and IIR are shareholders. All other authors declare no competing interests.

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