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Central venous access in oncology: ESMO Clinical Practice Guidelines†

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introduction

This guideline applies to central venous access in adult cancer patients, which includes peripherally inserted central catheters (PICCs), tunnelled central catheters and totally implantable devices. Since most evidence comes from the use of central venous catheters (CVCs) in patients with a diversity of pathologies, some recommendations are based on guidelines and studies which may lack some specificity for cancer patients.

central venous access: insertion

Long-term central venous access devices are essential in the management of oncology patients, as they minimise the discomfort of frequent venipuncture and cannulation.

There are four main classifications of CVCs [1, 2]:

- Non-tunnelled catheters, which are indicated for short-term use when peripheral venous access is unachievable.
- Tunnelled central catheters, used when long-term access (>30 days) is required for the administration of chemotherapy, antibiotics, parenteral feeding and blood products.
- Fully implantable or surgically implantable catheters (ports or port-a-caths), also provided for long-term use and associated with a low risk of infection. The device, which consists of a chamber (completely metallic, plastic or both) connected to a catheter, is placed under the skin. The catheter is threaded into the sub-clavian, jugular or femoral vein. The subcutaneous reservoir is placed in a pocket created in front of the pectoralis major muscle, in the sub-clavicular region. The reservoir is accessed via a specific needle through intact skin [3].
- PICCs are placed via a peripheral vein (i.e. basilica vein, brachial vein or less frequently cephalic vein) of the arm into the superior vena cava (SVC). Their main limitation is shorter longevity, due to a higher risk of thrombosis.

The main sites for central venous access devices are the internal jugular, external jugular and sub-clavian veins. Other potential access sites include: the cephalic vein in the deltopectoral groove, axillary vein and femoral vein. There is insufficient evidence to recommend a specific insertion site, but the femoral vein should be avoided unless there is a contraindication to the other sites (e.g. SVC syndrome), due to the increased risk of infection and concerns about thrombosis [I, A] [1, 4].

Careful preoperative assessment is advised. This should include the patient's medical history, a physical examination and the appropriate laboratory and radiological tests (discussed below).

Insertion of an implantable venous access device should be carried out under strict sterile conditions, in the operating room [II, B] [5, 6] and under local anaesthesia, with or without sedation. Chlorhexidine solutions with alcohol should be used [I, A] [7, 8].

Antimicrobial prophylaxis to prevent catheter colonisation, before insertion or during maintenance of CVCs, is not recommended [I, A] [9, 10].

Initial venous access can be carried out by using either the open or the percutaneous approach [11]. The open technique (cephalic vein cut-down) is the best approach to avoid the risk of immediate complications [IV, D] [12]. Randomised, controlled trials comparing 2D ultrasound to the surface landmark approach, for locating the internal jugular vein, report a higher first insertion attempt success rate, for 2D ultrasound [II, C] [13]. The data in the literature are equivocal on sub-clavian vein access [II, C] [14] and insufficient for femoral vein access [III, D].

Catheter tip position should be verified radiologically with an intraoperative fluoroscopy, or a post-operative chest X-ray [II, B] [15]. The desired location of the catheter tip is at the junction between the right atrium and SVC. An alternative to radiologic confirmation is the intracavitary electrocardiogram (ECG) method, where arrhythmia is documented during insertion of the wire [V, D] [16].

After the procedure, patients require 4 hourly observations including: temperature, pulse, blood pressure and respiratory rate. A chest X-ray is required if the patient has dyspnoea or chest wall pain [II, C] [17–19]. Implantable devices only require post insertion care until the incision has healed. Routine flushing with saline, after the completion of any infusion or blood sampling, is recommended [II, B] [1, 20].

To maintain patency of subcutaneous ports that are not in active use, a four weekly flush is recommended [III, C] [1, 20]. For tunnelled cuffed catheters and PICC lines, a weekly flush is

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also recommended [III, C]. There are some reports supporting an extended time for port flushing, i.e. every 8 weeks or every 3–4 months [21–23]. More research should be done to prospectively access the best time interval. An ongoing study is comparing flushing every 3 months to every 4-6 weeks (clinicaltrials.gov. Study NCT01047644).

immediate complications

Immediate complications occur at the time of the procedure, and usually consist of injury to the surrounding vital structures or malpositioning of the catheter tip. The most frequent immediate complications include: cardiac arrhythmia (23%–25%), accidental arterial puncture (0%–15%), haemothorax (0.1%–11%), pneumothorax (1%–4%) and air embolism (rare) [24].

In specific immediate complications, the following management is recommended:

- Cardiac arrhythmia: occurs during insertion if the catheter is fed too far in. Arrhythmias will be seen on the ECG monitor and corrected by pulling the catheter back.
- Accidental arterial perforation: remove the cannula and apply firm pressure for 10 min, monitor the neurological, haemodynamic and airway parameters during this time.
- Haemothorax: insertion of a large-bore chest tube to drain pleural blood is the mainstay of therapy for haemothorax [25, 26]. Thoracotomy is reserved for patients with a massive haemothorax [26, 27].
- Pneumothorax, diagnosed and confirmed with a chest X-ray: in patients with no spontaneous recovery, a chest tube should be inserted to facilitate drainage [28].
- Air embolism: immediately place the patient in the lateral decubitus head down position and deliver 100% oxygen [29].
- Catheter tip migration or breakage and migration: immediate management by interventional radiology for repositioning or removal.

CVC-related infection

The presence of an intravascular foreign body with direct communication to the outside environment will increase the patient's risk of infection. Infection remains the most common complication in cancer patients with indwelling CVCs [30]. Catheter-related bloodstream infections (CRBSIs) contribute to treatment delays, reduced doses of chemotherapeutics and consequently suboptimal treatment, prolonged hospitalisations, higher mortality rate and increased costs of care [31, 32].

A CVC infection is defined as any infection related to a vascular catheter, including local (at the insertion site) and systemic infections (bloodstream), which have positive cultures [33]. A CRBSI is a primary blood stream infection (BSI) that occurs when bacteria enters the bloodstream through the central line. In the United States, the reported rate of CRBSI in patients with cancer is 1.5 per 1000 CVC/days, with a mortality rate of 12%–25% [31, 34]. A recent retrospective analysis from the Surveillance, Epidemiology and End Results Programme [35] conducted in cancer patients over 65 years of age, revealed a threefold increase in infection risk when compared with previously reported literature. This risk was independent of patient, disease and treatment characteristics. Additionally, as has been reported in previous studies, lower infection rates were seen in patients with implanted catheters versus tunnelled catheters and PICCs.

CRBSI is the most common cause of nosocomial bacteraemia [36]. Every year, almost 6000 patients in the UK acquire a CRBSI [30, 37]. The risks for acquiring a CRBSI can be endogenous, such as patient age, disease background and comorbidities or exogenous, such as the type of CVC used and the insertion technique applied [37]. A study by Mollee et al. [38] of 727 patients revealed an overall CRBSI rate of 2.5 per 1000 line/days. It is noted that different types of CVCs are associated with different levels of infection risk: implantable ports have the lowest incidence of CRBSI; the highest incidence of infection is found in non-tunnelled CVCs. In addition to the type of CVC used, the patients' diagnosis can be an added risk factor. For example, patients diagnosed with aggressive haematological malignancies are associated with the highest risk of BSI [38]. Overall, CRBSI occur in 3% of catheterisations; however, the incidence may be as high as 16% [36]. In a study by Toure et al. [39], which evaluated 315 consecutive patients, CRBSI occurred in 41 patients (13%). This study elicited four independent risk factors: World Health Organisation performance status, pancreatic cancer, parenteral nutrition administration and cumulative catheter utilisation-days in the previous month. Finally, a recent case–control study [40] that included patients with solid tumours and only implantable central venous ports identified prolonged catheter stay as a risk factor for port-related BSI infections.

For short-term CVCs (<30 days of dwell time), the major cause of CRBSI is the migration of skin microorganisms from the insertion site along the external surface of the catheter. For long-term CVC, the hub and the lumen of the CVC is the most common source of infection. The colonising microorganisms embed themselves in a microbial biofilm within 48–72 h of insertion. They may develop resistance to traditional systemic antibiotics, becoming difficult to eradicate and a recurrent cause of CRBSI [31].

Historically, the most common BSI pathogens were Gram-negative bacteria. Due to the widespread use of indwelling catheters over the past three decades, the proportion of Gram-positive microorganisms has risen in most cancer centres. Gram-positive bacteria cause ~60% of BSIs, Gram-negative bacteria account for ~25% and fungi around 10% [41]. CRBSI are most frequently caused by coagulase-negative staphylococci, *Staphylococcus aureus* and *Candida* spp. [2]. The less frequent pathogens are: *Bacillus* spp., enterococci, mycobacteria and non-lactose fermenting Gram-negative bacilli [2].

diagnosis of CVC infections

CVCs infections can be classified into:

- Localised infections in the entrance of the catheter.
- Infections of the tunnel/port-pocket.
- CRBSI [2].

It is rare that the infusate is the source of infection. Possible complications due to haematogenous seeding are: endocarditis, suppurative thrombosis, osteomyelitis and metastatic site infections.

Clinical manifestations of CVC infection may include: fever, inflammation or purulence at the insertion site (erythema,

tenderness, pain, induration and drainage), catheter dysfunction, hypotension, chills and signs of sepsis of sudden onset, after catheter use.

In the diagnostic assessment, blood cultures are indicated before starting antibiotic treatment [I, A] [2]. If CRBSI is suspected, paired blood samples should be obtained (acquiring the same volume of blood) from the catheter and from a peripheral vein [II, A] [2]. If it is not possible to acquire peripheral vein cultures, two blood samples should be drawn (at different times) from two different catheter lumens [III, B] [2]. There is no good evidence to recommend collecting cultures from all catheter lumens [III, C]. When preparing the skin (and CVC ports) to collect cultures, alcohol, iodine tincture or alcoholic chlorhexidine (10.5%) should be used, rather than povidone–iodine [I, A] [2]. It is important to leave adequate time for the skin to dry in order to avoid blood contamination [I, A] [2].

If there is exudate at the exit site of the catheter, a swab should be taken of the exudate for culture and gram staining [III, B] [2]. When the catheter is removed, the catheter tip should be cultured rather than the subcutaneous segment. For subcutaneous ports, a culture of the material inside the port reservoir should be included, as it is more sensitive than the catheter tip culture. The most reliable diagnostic techniques are semiquantitative (roll plate) or quantitative catheter culture (luminal flushing or sonication methods).

CRBSI is considered, in cases of BSI, when there are no other sources of bacteraemia and there has been a CVC *in situ* for longer than 2 days. Microbiological results will reveal either a positive culture of the same organism from the catheter tip or at least one percutaneous blood culture [I, A]. They could also reveal a culture of the same organism, from at least two blood samples (catheter hub and peripheral vein) on quantitative blood cultures or criteria meeting differential time to positivity (DTP) [II, A] [2, 42].

The criteria for CRBSI in quantitative blood cultures is a colony count from the catheter hub sample ≥3-fold higher than the colony count from the peripheral vein sample (or a second lumen) [43]. If semiquantitative cultures are used, the result should be >15 CFU/ml of the same microbe from the insertion site, hub site and peripheral blood culture. When quantitative cultures are not available, DTP should be applied, i.e. growth from the catheter hub at least 2 h before growth detected from the peripheral vein sample [2]. Sensitivity for this diagnostic test has been reported to be 85% with a specificity of 91% [44].

treatment of CVC infections

Treatment decisions should take into account: the patient's disease status, comorbidities, the type of catheter, exit site infection or CRBSI, previous exposure to antibiotics, severity of myelosuppression and signs of tunnel or port infection (Figure 1).

Empiric antibiotic therapy should be started when there are clinical signs of infection. Antibiotic therapy onset should not be delayed for blood culture results to be available. Since the most frequent infectious agents are Staphylococcus coagulase-negative and *S. aureus* methicillin-resistant (MRSA), the recommended treatment is vancomycin [II, A] [45–48]. Daptomycin can be used in cases of higher risk for nephrotoxicity or in high prevalence of MRSA strains, with vancomycin minimum inhibitory concentration (MIC) ≥2 μg/ml [II, A] [49–51]. Linezolide is not recommended for empirical use [I, A] [2].

In cases that present with severe symptoms (sepsis, neutropaenia), empirical use of anti-Gram-negative bacilli antibiotics, such as fourth-generation cephalosporins, carbapenem or β-lactam/β-lactamase combinations with or without an aminoglycoside, is recommended [II, A]. The selection of the type of antibiotic should be guided by the antimicrobial susceptibility testing (AST) data of each institution [II, A] [2].

Drug resistance is a significant problem and is an important risk factor especially in patients with haematological conditions, the severely immunocompromised and those who have had prolonged exposure to antibiotic therapy. The most frequent pathogens in this setting are *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. [41, 52]. In cases identified to be at risk of colonisation by a drug-resistant pathogen, the appropriate treatment is recommended (please refer to Table 1) [II, A] [2]. For example, known risk factors for carbapenem resistance are: older age, prolonged neutropaenia, presence of indwelling CVC, haematological malignancy, previous use of cefepime and total parenteral nutrition [III, C]. In this scenario, combined based therapy is recommended [54–56].

The recommended empirical treatment of candidaemia in critically ill patients is an Echinocandin (caspofungin, micafungin, anidulafungin), if one of the following risk factors is present: haematological malignancy, a recent bone marrow transplant or a solid organ transplant, presence of femoral catheters, colonisation of *Candida* spp. at multiple sites or prolonged use of broad spectrum antibiotics [III, A] [2, 57, 58]. Fluconazole can be used if the patient is clinically stable, has had no exposure to azoles in the previous 3 months and if the risk of *C. krusei* or *C. glabrata* colonisation is low [III, A] [2, 59].

In cases of neutropaenia, antibiotic treatment recommendations should follow published guidelines for this setting [60].

Once empirical treatment has been initiated the following steps are recommended:

- Decide if the indwelling catheter should be removed or preserved.
- Tailor antibiotic treatment to culture results (see Table 1).
- Decide on treatment duration.

indications for CVC removal

Removal of the CVC is indicated at the diagnosis of [II, A] [2]:

- severe sepsis
- suppurative (septic) thrombophlebitis
- endocarditis
- tunnel infection
- port abscess
- BSI which continues despite 48–72 h of adequate coverage; or infections with *S. aureus*, fungi or mycobacteria.

Pathogens which have a high risk for infection recurrence and may need catheter removal are: *Bacillus* spp., *Corynebacterium jeikeium*, *Stenotrophomonas maltophilia*, *Pseudomonas spp*, and *Enterococcus* resistant to vancomycin [61–63]. In patients where catheter salvage is attempted, antibiotic lock therapy (ALT), in

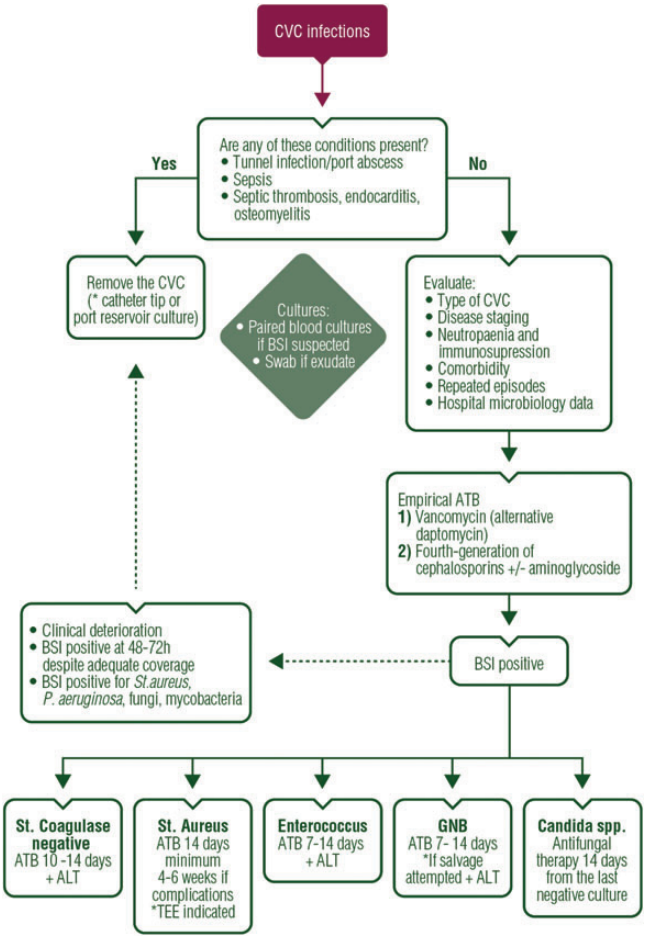

Figure 1. Management of central venous catheter infections. CVC, central venous catheter; BSI, blood stream infection; P, *Pseudomonas*; St., *Staphylococcus*; ATB, antibiotic treatment; ALT, antibiotic lock therapy; GNB, Gram-negative bacillus; TEE, trans-oesophageal echocardiogram; spp., species.

addition to systemic therapy, is indicated [II, B] [2, 64]. There is less clear evidence for the efficacy of the administration of antibiotics through the colonised catheter, instead of ALT [III, C] [2].

antibiotic lock therapy

ALT is the instillation of highly concentrated antibiotic (100–1000 times planktonic MIC) in the CVC, in order to achieve therapeutic concentrations sufficient to eliminate the susceptible pathogens in the biofilm. Usually, the solution is combined with an anticoagulant [low-dose heparin or ion chelators, such as citrate or ethylenediaminetetraacetate (EDTA)] that will be dwelling or 'locked' in the catheter whenever it is not in use.

ALT is indicated for the prevention and treatment of CVC infections. When ALT is used to treat infection, no signs of exit site or tunnel infection should exist [II, B] [2, 64, 65]. If peripheral blood cultures are negative and the isolated pathogens from the catheter are Staphylococcus coagulase-negative or Gram-negative, ALT can be used on its own. Otherwise, in cases of proven CRBSI, ALT is to be used in combination with systemic antibiotic therapy throughout the duration of the systemic treatment.

Success rates of catheter salvage are reported to be 77% [64, 65]. Some studies show that early initiation of ALT (first 48–72 h) is associated with better outcomes, in terms of infection complications and catheter salvage [66]. Treatment duration has been recommended to be 7–14 days [III, B] [2], but some authors suggest a shorter course of therapy (72 h) [67]. Ideally dwell time should be ≥12 h (minimum of 8 h per day) [III, C] [64, 68] and should not exceed 48 h before reinstallation [2].

Systemic exposure to higher levels of the solution components (mainly if it is flushed and not locked) is a potential risk associated with ALT. Other side-effects include: ototoxicity associated with aminoglycoside use, bleeding after higher exposure to anticoagulants (heparin 1000 units/ml or citrate 30%–46.7%), hypocalcaemia and arrhythmias (associated with higher concentrations of citrate), catheter occlusion and increased risk of antibiotic resistance [64]. A recent meta-analysis [69] revealed that anticoagulant citrate is associated with higher efficacy in the prevention of CRBSI and a lower risk of bleeding compared with heparin, but there is a higher risk of arrhythmias due to induced hypocalcaemia. Currently, a lower concentration (solution of citrate 4%) is recommended and is available in Europe [70, 71]. The benefits of ALT outweigh the reported risks, but local protocols for ALT use should be carefully implemented.

treatment duration

The duration of treatment will depend on the response to treatment in the first 48 or 72 h (i.e. resolution of clinical symptoms

Table 1. Antibiotic treatment of CVC-related infections

	Pathogen	Systemic treatment	ALT
Gram-positive	*S. aureus*	Methicillin-susceptible: Nafcillin or oxacillin Or Cefazolin or vancomycin	Vancomycin, 1–5 mg/ml, heparin unnecessary Daptomycin 2.5 mg/ml, diluted in lactated Ringer's solution
		Methicillin-resistant Vancomycin Or Daptomycin or linezolid	Taurolidine 2.5 ml, either combined with 4% sodium citrate, sodium heparin 2500 IU or with 25 000 IU urokinase Gentamicin 5 mg/ml plus EDTA 30 mg/ml, for 3–5 days, in addition to systemic vancomycin
	S. coagulase-negative	Methicillin-susceptible Nafcillin or oxacillin Or First-generation cephalosporin or vancomycin Methicillin-resistant Vancomycin or Daptomycin, linezolid or quinupristin/dalfopristin	Vancomycin 1–5 mg/ml, added to heparin 2500–5000 IU/ml, lock for 12 h/day Daptomycin 5 mg/ml, diluted in lactated Ringer's solution. Duration of lock from 12 to 18 h/day 74% ethanol 3 ml, combined with 1 ml 0.9% NaCl. Lock 20–24 h/day
	E. faecalis/E. faecium	Ampicillin-susceptible Ampicillin (or penicillin) ± gentamicin Or Vancomycin Ampicillin-resistant, Vancomycin-susceptible Vancomycin ± gentamicin Or Linezolid or daptomycin Ampicillin-resistant, Vancomycin-resistant Linezolid or daptomycin Or Quinupristin/dalfopristin	Taurolidine 2.5 ml, either combined with 4% sodium citrate, sodium heparin 2500 IU or with 25 000 IU urokinase Gentamicin 5 mg/ml plus tetrasodium EDTA 30 mg/ml for 1 day, in association with systemic vancomycin
Gram-negative	*Escherichia coli* and *Klebsiella* spp.	ESBL-negative: Third-generation cephalosporin (e.g. ceftriaxone) Or Ciprofloxacin or aztreonam ESBL-positive: Carbapenem (e.g. ertapenem, imipenem, meropenem or doripenem) Or Ciprofloxacin or aztreonam	Ciprofloxacin or amikacin, both at the dose of 2 g/l, plus heparin 20 IU/ml Taurolidine 2.5 ml, either combined with 4% sodium citrate, sodium heparin 2500 IU or with 25 000 IU urokinase Gentamicin 5 mg/ml plus EDTA 30 mg/ml for 3 days, combined with systemic gentamicin
	Enterobacter spp. and *Serratia marcescens*	Carbapenem (e.g. ertapenem, imipenem or meropenem) Or Cefepime or ciprofloxacin	
	Acinetobacter spp.	Ampicillin/sulbactam or carbapenem (e.g. imipenem or meropenem)	
	Stenotrophomonas maltophilia (*)	TMP-SMZ Or Ticarcillin-clavulanate	
	Pseudomonas aeruginosa	Fourth-generation cephalosporin (cefepime) or carbapenem (imipenem or meropenem) or piperacillin-tazobactam, with or without aminoglycoside (tobramycin)	
	Burkholderia cepacia (*)	TMP-SMZ or carbapenem (imipenem or meropenem)	

Continued

Table 1. *Continued*

	Pathogen	Systemic treatment	ALT
Fungi	*C. albicans*	Azoles : Fluconazole, Voriconazole Or Echinocandins: caspofungin, anidulafungin, micafungin (first-line treatment if high rate of fluconazole-resistant *C. glabrata* and *C. krusei*)	Liposomal Amphotericin B 1 mg/ml ABLC 2 mg/ml, plus EDTA 30 mg/ml Caspofungin 2 mg/l Ethanol 25%–60% Duration of anti-fungal lock varies between 6 and 24 h/day The combination of ABLC and EDTA is the most effective against *Candida* biofilms

(*) few data on ALT for these agents.
Adapted from Band JD. Treatment of intravascular catheter-related infections. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 2015)
Additional references [2, 53].
C, Candida; ABLC, amphotericin B lipid complex; ALT, antibiotic lock therapy; ESBL, *Enterococcus* Staphylococci Extended spectrum β-lactamase; TMP-SMZ, trimethoprim–sulfamethoxazole; CVC, central venous catheter; EDTA, ethylenediaminetetraacetate; NaCl, sodium chloride; S, staphylococcus; E, enterococcus; spp., species.

and negative cultures), the type of pathogen and the presence of complications. In most cases, 10–14 days of treatment is recommended after signs of infection have resolved [2] (the day of the first negative cultures is day one)—'see specific pathogens'. If positive cultures are present 72 h after catheter removal or when complications occur [i.e. endocarditis or suppurative (septic) thrombophlebitis], 4–6 weeks of treatment is recommended [II, A for *S. aureus* infection; III, C for infection due to other pathogens]. In case of osteomyelitis, treatment should be 6–8 weeks in duration [II, A] [2].

staphylococcus coagulase-negative

This is the most frequent and more benign pathogen associated with CRBSI, except for *S. lugdunensis* which should be managed as a *S. aureus* infection. Since it is the most frequent contaminant, diagnosis should be based on more than one set of positive blood cultures, and preferentially from the catheter and peripheral vein [II, A] [2]. If there are no complications attempts should be made to salvage the catheter with systemic antibiotic therapy for 10–14 days, including ALT [II, B] [2] (see Table 1). A recent meta-analysis shows that the benefit of ALT is higher for this pathogen, with more data available on the use of daptomycin [53]. If the catheter is removed antibiotic treatment should be continued for 5–7 days [2, 31].

staphylococcus aureus

The mortality of patients with *S. aureus* bacteraemia is increasing over time, as is the prevalence of MRSA infections [Methicillin-sensitive *S. aureus* (MSSA) increased from 3.6% to 51.7%, and MRSA from 0% to 83.3% between 1980 and 2000] [72]. *Staphylococcus aureus* infections are more frequent in older people and most commonly caused by colonisation of intravenous catheters [73]. The strongest predictors for mortality are pneumonia and the absence of an identified infective focus. Other predictors are inadequate antimicrobial therapy and identification and removal of the infective focus. The presence of: malignancy, diabetes, high serum glucose level, methicillin resistance, serum albumin level, interleukin-10 and C-reactive protein are also considered risk factors, but need to be prospectively validated [74].

In cases of *S. aureus* infection, the catheter should be removed and antibiotic systemic therapy implemented [II, B] [2, 31] (see Table 1). Treatment should proceed for a minimum of 14 days (when there is a response), and 4–6 weeks in cases of haematogenous complications or persistent bacteraemia after catheter removal [II, B] [2, 31]. Due to the high risk of endocarditis (25%–32%), a trans-oesophageal echocardiogram (TEE) is indicated unless, at 72 h after catheter removal, cultures and clinical assessments are negative [2, 75, 76]. TTE should be carried out at 5–7 days after the onset of bacteraemia [III, B]. The known risk factors for haematogenous complications [77] are: prosthetic intravascular devices, cardiac valvular disease, immune-compromising conditions (diabetes, medications, acquired immune deficiency syndrome), delayed catheter removal and suppurative thrombophlebitis. The success rate for ALT is low and it should only be used if there are major contraindications for catheter removal such as no alternative venous access, bleeding diathesis or quality-of-life issues related to changing the catheter to a different location. If used, ALT should be combined with systemic therapy for at least 4 weeks [II, B] [2, 31, 76]. Adjunctive rifampicin in *S. aureus* bacteraemia in the mechanism of enhanced early bacterial killing is currently being studied in a randomised trial [78]. For antibiotic treatment, see Table 1.

enterococcus

European data reveal that enterococcus bacteraemia is responsible for 7.2% of BSI [79]. A recent Spanish study evaluated the incidence of BSI by this pathogen (over an 8-year period) and found that it was responsible for 6% of all episodes, with a 17% increase of the annual incidence (95% confidence interval 19%–21%) [80]. In cases of *Enterococcus* infection, the catheter can be

retained and systemic antibiotic therapy is recommended [II, B] [2, 31]. The preferred antibiotic is ampicillin, but vancomycin should be used in cases of resistance [III, A] [2]. In third-line treatment linezolid or daptomycin are recommended and should be used according to AST data [II, B] [2]. Combination therapy is not superior to monotherapy, unless it is used in an attempt to salvage the catheter. In this case, systemic antibiotic therapy (gentamicin+ampicillin) should be combined with ALT. The duration of treatment should be 7–14 days, if no endocarditis or metastatic infection sites are present. The risk of endocarditis is higher with *Enterococcus faecalis* than with *E. faecium*, but TEE should only be carried out if clinical signs of endocarditis are present [III, B] [2, 81].

gram-negative bacillus

Systemic antibiotic therapy is indicated [II, A] [2] (see Table 1). If catheter salvage is attempted ALT should be used [III, C] [2]. Combined antibiotic therapy should be used in patients with recent infection or colonisation with multidrug-resistant (MDR) Gram-negative bacteria [II, A] [2]. There is concern about the emergent resistance of Gram-negative bacillus in haematology patients. A recent prospective cohort study of 574 BSI in Italian haematology patients, showed Enterobacteriaceae resistance to third-generation cephalosporins in 36.9%, *K. pneumoniae*-resistant strains to carbapenems in 34.9% and *P. aeruginosa* isolates MDR in 69.7% [52].

candida

Candidaemia has mainly been studied in haematology patients [82] (leukaemia or myelodysplastic syndrome represent 40%–50% of malignancies with invasive fungal diseases), but there are also reports in solid tumours [83]. Besides malignancy, other identified risk factors were: the presence of CVCs, neutropaenia, immunosuppressive agents, broad spectrum antibiotic use and parenteral nutrition. There is a 30% association with bacteraemia, mainly antibiotic-resistant pathogens such as MRSA, vancomycin-resistance enterococci, extended spectrum β-lactase *Escherichia coli* and MDR *A. baumannii* [83–85]. Additionally, mortality has been reported at 30%–50% [57, 85–87]. Most cases are related to *Candida albicans* [88], but there is a tendency for an increase in non-albicans as well as resistance to azoles [57, 84].

When fungi infection is present, the CVC should be removed [II, A] [2] and anti-fungal therapy should be initiated [II, A] (see Table 1). Some evidence reveals an improved survival when these measures are implemented in the first 48–72 h [III, A] [66, 89]. Amphotericin is less used because of issues surrounding toxicity and it having a similar efficacy to echinocandins [58]. Although limited data are available, ALT demonstrates the best results when used with amphotericin, ethanol or echinocandins, but generally ALT is not effective in Candida CRBSI [III, C] [2, 90].

prevention of CVC-related infections

CRBSI is an iatrogenic problem that causes significant morbidity and mortality. CRBSIs are responsible for longer lengths of hospital stays and increased treatment costs [37]. The adherence to preventive measures has a significant impact on reducing the risk of CVC-related infections [31]. The 2011 update of the Centre for Disease Control guidelines, for the prevention of intravascular catheter-related infections, introduces several recommendations, including specific instructions on: the size of catheter implantation, dressing, protective clothing, handling and maintenance of the CVCs [4].

The main strategies for the prevention of CRBSIs are [I, A] [33, 91]:

- Education and ongoing training of health care personnel who insert and maintain catheters.
- Use of maximal sterile barrier precautions during CVC insertion.
- Use of >0.5% chlorhexidine skin preparation with alcohol for antisepsis.
- Avoidance of routine replacement of CVCs as a strategy to prevent infection.
- Use of antiseptic/antibiotic-impregnated short-term CVCs and chlorhexidine-impregnated sponge dressings, if the rate of infection is not decreasing despite adherence to other strategies.

Table 2. Potential risk factors for catheter-related thrombosis

Patient-related	Biomarker	Treatment-related	Catheter-related	Technical-related	Vessel-related
Advanced age	Hb <10 g/dl	Chemotherapy	Size	Insertion technique	Type of vessel
Race	WBC >11 × 10^9/l	Endocrine therapy	Number of lumen	Left-sided insertion	Diameter
Male	Platelet ≥350 × 10^9/l	Radiotherapy	Material	Multiple attempts	Trauma
Obesity	D dimer	Anti-angiogenesis	Type of catheter	Previous catheterisation	
Smoking habit	Tissue factors: soluble P selectin	Supportive therapy (erythropoietins; transfusion)	Position of the tip		
Previous history of VTE	Factor VIII		CVC-related infection		
Immobilisation	Prothrombin	Surgery	Presence of valves		
Comorbidities	Fragment F1+2				
Thrombophilic states					
Mucin-producing cancer					
Cancer histology					
Tumour primary site					
Time after initial diagnosis of cancer					
Advanced tumour stage					

VTE, venous thromboembolism; Hb, haemoglobin; WBC, white blood cell; CVC, central venous catheter.

Table 3. Comparison of Guidelines recommendations for the treatment of catheter-related thrombosis

	NCCN	ASCO	ACCP	SOR
Treatment				
Initial	LMWH: Dalteparin 200 U/kg o.d. Enoxaparin 1 mg/kg b.i.d. Tinzaparin 175 U/kg o.d. Fondaparinux 5 mg (<50 kg); 7.5 mg (50–100 kg); 10 mg (>100 kg o.d.) APTT-adjusted UFH infusion	LMWH is recommended for the initial 5–10 days of treatment of DVT and PE in patients with a CrCl >30 ml/min Installation of 2-mg-t-PA is recommended to restore patency and preserve catheter function	Initial treatment with UFH, LMWH or fondaparinux rather than VKA	LMWH for a minimum of 3 months VKA can be considered
Long term	LMWH is recommended for first 6 months as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer Warfarin 2.5–5 mg every day initially (INR value target 2–3)	LMWH is recommended VKAs are acceptable (INR 2–3) if LMWH is not available 3–6 months of anticoagulation therapy with LMWH or LMWH followed by warfarin (INR 2–3) is recommended for treatment of symptomatic CVC thrombosis	LMWH preferred to VKA In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban Patients receiving extended therapy should continue with the same agent used initially	Insufficient evidence to support extended therapy
Duration	As long as the catheter is in place 1–3 months after catheter removal Indefinite anticoagulant if active cancer or persistent risk factors	Extended therapy with LMWH or VKA beyond 6 months if: Metastatic disease Active chemotherapy Recurrent thrombosis	Extended therapy is preferred to 3 months of treatment	As long as the catheter is in place, active chemotherapy, active cancer
Thrombolytic therapy	Catheter-directed; If massive DVT	Not described	Catheter-directed; If low risk of bleeding and severe symptoms	Catheter-directed or systemic; if poorly tolerated vena cava syndrome
Catheter removal	If symptoms or thrombosis persist. If catheter is not required	Not described	If unfavourable clinical evolution under anticoagulation	If non functional Distal catheter tip not in the right position Infected thrombophlebitis Unfavourable clinical evolution under anticoagulation

Adapted from [107, 112, 132].

ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; b.i.d., twice-daily; DVT, deep vein thrombosis; INR, international normalised ratio; LMWH, low molecular weight heparin; o.d., once-daily; NCCN, National Comprehensive Cancer Network; PE, pulmonary embolism; SOR, Standards, Options and Recommendations methodology; VKA, vitamin K antagonist; APTT, activated partial thromboplastin time; UFH, unfractionated heparin; CrCl, creatinine clearance; t-PA, tissue plasminogen activator; CVC, central venous catheter.

NCCN Clinical Practice Guidelines in Oncology; Cancer associated Venous Thromboembolic Disease; http://www.nccn.org/professionals/physician_gls/pdf/vte.pdf [62, 135, 136].

- Implementation of bundled strategies, including documenting and reporting rates of compliance of all components of the bundle, as benchmarks for quality assurance and performance improvement.
- Implementation of appropriate patient education programmes, which include instructions on hand decontamination and the prevention of cross-contamination in patients with stomas [1, 2].

It is routine practice to flush tunnelled cuffed catheters and PICC lines weekly, and subcutaneous ports 4-weekly (when not in use), using heparin or normal saline 0.9% solution. An aseptic technique by hospital-trained nurses, which includes the use of alcoholic chlorhexidine 2% cleanser, to decontaminate catheter hubs before use, should be used [37, 92].

There is emergent evidence that the new generation of needleless connectors, which have mechanical valves that generate negative, positive or neutral pressure during disconnection, is associated with increased rates of CRBSI, mostly in intensive care units, but also oncology units [93–95]. The utilisation of neutral pressure mechanical valve connectors to avoid the risk of infection is recommended [III, C].

The use of antibiotic-coated catheters, which can be impregnated with antiseptics (chlorhexidine, silver sulfadiazine) or antimicrobials (minocycline/rifampin), has shown some advantage over non-coated CVCs in published systematic reviews [96, 97]. Due to methodological issues in these studies, however, a strong recommendation for their use is not warranted [II, B], although they could be useful in institutions where there are high rates of BSIs.

ALT solutions have been proposed in cases with a history of multiple CRBSI (despite appropriate CRBSI prevention measures) when the catheter is projected to remain *in situ* for longer than 7–8 weeks [II, B] [4]. The decision to use ALT should always take into account the possible side-effects discussed in the ALT section of this guideline. Chelator-based antimicrobial locks, in particular the combination of EDTA/minocycline, have been proven to be effective in patients with cancer and in patients on haemodialysis who have long-term CVCs [98–100]. The addition of 25% ethanol to a minocycline/EDTA lock solution demonstrated high efficacy in eradicating pathogens in the biofilm and high clinical efficacy in salvaging CVCs. Nitroglycerine citrate lock, which is a non-antibiotic chelator lock, also has proven efficacy [101]. More recently, a meta-analysis [102] assessed 2896 patients (the majority undergoing haemodialysis but some studies included oncology patients), showing that ALT was responsible for a 69% reduction of CRBSI, when compared with heparin. There was no change in the all-cause mortality and no difference among the antimicrobial solutions used. A Cochrane review on prophylactic antibiotics in oncology patients with long-term CVCs [10] also showed that flushing or locking with a combined antibiotic and heparin solution significantly reduced the risk of CRBSI Gram-positive sepsis.

catheter-induced thrombosis

Apart from infections, the main complication of CVCs is thrombosis [103]. Patients with cancer have a five to seven times elevated risk of thrombosis. The underlying causes are: activation of the coagulation cascade by cancer cells (increase of plasma thrombin levels and activity), decreased levels of coagulation inhibitors, impaired fibrinolysis, increased antiphospholipid antibodies, activated protein C-resistance and enhanced platelet aggregation [104]. Training of health care personnel, as well as appropriate patient education, is fundamental to reduce the risk of thrombosis. Risk reduction of venous thromboembolisms (VTEs) is important because VTEs are a detrimental factor for cancer survival [105]. CVC-related thrombosis (CRT) is detected

Table 4. Comparison of Guidelines recommendations for the prevention of catheter-related thrombosis

	NCCN	ASCO	ACCP	SOR
Prophylaxis				
Pharmacological	Not described	Routine prophylaxis is not recommended; routine flushing of the CVC with saline to prevent fibrin build up is recommended. Routine use of thrombolytic agents is not recommended	Prophylactic dose of LMWH or low-dose warfarin is not recommended	Prophylactic dose of LMWH or low-dose warfarin is not recommended
Mechanical	Not described	May be added to pharmacologic therapy, but not used alone to prevent VTE unless anticoagulants are contraindicated	Not described	The distal tip of the CVC should be placed at the junction between the superior vena cava and the right atrium. Right-sided insertion and placement of the CVC in a specialised unit should be done.

ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; CVC, central venous catheter; NCCN, National Comprehensive Cancer Network; SOR, Standards, Options and Recommendations methodology; VTE, venous thromboembolism; LMWH, low molecular weight heparin.

Table 5. Summary of recommendations

Central venous access—insertion

- Fully implantable or surgically implantable catheters are associated with a low risk of infection
- Insertion in the femoral vein should be avoided, due to the increased risk of infection and thrombosis [I, A]
- Insertion of an implantable venous access device should be carried out under strict sterile conditions, in the operating room [II, B]
- Chlorhexidine solutions with alcohol should be used [I, A]
- Antimicrobial prophylaxis is not recommended [I, A]
- Initial venous access can be carried out either by using the open or percutaneous approach. The open technique (cephalic vein cut-down) is the best approach to avoid the risk of immediate complications [IV, D]
- Catheter tip position should be verified radiologically with an intraoperative fluoroscopy or a post-operative chest X-ray [II, B]
- An alternative to radiologic confirmation is the intracavitary ECG method, where arrhythmia is documented during insertion of the wire [V, D]
- After the procedure, patients require 4 hourly observations including: temperature, pulse, blood pressure and respiratory rate. A chest X-ray is required if the patient has dyspnoea or chest wall pain [II, C]
- Routine flushing with saline, after the completion of any infusion or blood sampling, is recommended [II,B]
- To maintain patency of subcutaneous ports not in active use, a four weekly flush is recommended [III, C]
- For tunnelled cuffed catheters and PICC lines, a weekly flush is recommended [III, C]

Catheter-related infection—diagnosis

- Blood cultures are indicated before starting antibiotic treatment [I, A]
- If CRBSI is suspected, collect paired blood (acquiring the same volume of blood) from the catheter and from a peripheral vein [II, A]
- If it is not possible to acquire peripheral vein cultures, two blood samples should be drawn (at different times) from two different catheter lumens [III, B]
- There is no good evidence to recommend collecting cultures from all catheter lumens [III, C]
- Alcohol, iodine tincture or alcoholic chlorhexidine (10.5%) should be used, rather than povidone–iodine for skin preparation before collection [I, A]
- It is important to leave adequate time for the skin to dry in order to avoid blood contamination [I, A]
- If there is exudate at the exit site of the catheter, a swab should be taken of the exudate for culture and Gram staining [III, B]

Catheter-related infection—treatment

- Treatment decisions should be based on: the patient's disease status, comorbidities, the type of catheter, exit site infection or CRBSI, previous exposure to antibiotics, severity of myelosuppression and signs of tunnel or port infection
- If CRBSI is suspected empirical antibiotic treatment with vancomycin is recommended before blood culture results are available [II, A]
- Daptomycin can be used in cases of higher risk for nephrotoxicity or in high prevalence of MRSA strains, with vancomycin MIC ≥2 μg/ml [II, A]
- Linezolide is not recommended for empirical use [I, A]
- If severe symptoms are present empirical use of anti-Gram-negative bacilli antibiotics (fourth-generation cephalosporins, carbapenem or β-lactam/β-lactamase combinations with or without an aminoglycoside) is recommended [II, A]
- The selection of the type of antibiotic should be guided by the AST data of each institution [II, A]
- Empiric antibiotic treatment should also take into account the risk for drug-resistant strains [II, A]. Antibiotic treatment should be adjusted to blood cultures results
- The recommended empirical treatment of candidaemia in critically ill patients is an Echinocandin (caspofungin, micafungin, anidulafungin), if one of the following risk factors is present: haematological malignancy, a recent bone marrow transplant or a solid organ transplant, presence of femoral catheters, colonisation of *Candida* spp. at multiple sites or prolonged use of broad spectrum antibiotics [III, A]
- Fluconazole can be used if the patient is clinically stable, has had no exposure to azoles in the previous 3 months and if the risk of *C. krusei* or *C. glabrata* colonisation is low [III, A]

Indications for CVC removal

- Indications to remove the CVC are: severe sepsis, suppurative (septic) thrombophlebitis, endocarditis, tunnel infection, port abscess, BSI which continues despite 48–72 h of adequate coverage or infections with *S. aureus*, fungi or mycobacteria [II, A]

Antibiotic lock therapy

- In patients where catheter salvage is attempted, ALT, in addition to systemic therapy, is indicated [II, B]
- ALT is indicated for prevention and treatment of CVC infections. In this last case, no signs of exit site or tunnel infection should exist [II, B]
- ALT: Treatment duration has been recommended to be 7–14 days [III, B]
- ALT: Ideally dwell time should be ≥12 h (minimum of 8 h per day) [III, C] and should not exceed 48 h before reinstallation

Treatment duration

- In most cases 10–14 days of treatment is recommended after resolution of signs of infection (II, B)
- If positive cultures are present 72 h after catheter removal or when complications are present [i.e. endocarditis or suppurative (septic) thrombophlebitis], 4–6 weeks of treatment is recommended [II, A for *S. aureus* infection; III, C for infection due to other pathogens] In case of osteomyelitis, treatment should be 6–8 weeks in duration [II, A]

Continued

Table 5. *Continued*

Staphylococcus coagulase-negative

- Diagnosis should be based on more than one set of positive blood cultures, and preferentially from the catheter and peripheral vein [II, A]
- If there are no complications, attempts should be made to salvage the catheter with systemic antibiotic therapy for 10–14 days, ALT [III, B]

Staphylococcus aureus

- In cases of *S. aureus* infection, the catheter should be removed and antibiotic systemic therapy implemented [II, B]
- Treatment should proceed for a minimum of 14 days (when there is a response), and 4–6 weeks in cases of haematogenous complications or persistent bacteraemia after catheter removal [III, B]
- Due to the high risk of endocarditis (25%–32%), a TEE is indicated unless, at 72 h after catheter removal, cultures and clinical assessments are negative. TEE should be carried out at 5–7 days after the onset of bacteraemia [III, B]
- If used, ALT should be combined with systemic therapy for at least 4 weeks [II, B]

Enterococcus

- In cases of *E.* infection the catheter can be retained and systemic antibiotic therapy is recommended [II, B]
- The preferred antibiotic is ampicillin, but vancomycin should be used in cases of resistance [III, A]
- In third-line treatment linezolid or daptomycin are recommended and should be used according to AST data [II, B]
- The risk of endocarditis is higher with *E.* faecalis than with *E.* faecium, but TEE should only be carried out if clinical signs of endocarditis are present [III, B]

Gram-negative bacillus

- Systemic antibiotic therapy is indicated [II, A]
- If catheter salvage is attempted ALT should be used [III, C]
- Combined antibiotic therapy should be used in patients with recent infection or colonisation with MDR GNB [II, A]

Candida

- When fungi infection is present, the CVC should be removed [III, A] and anti-fungal therapy should be initiated [II, A]

Catheter-related infection—prevention

Main strategies:

- Education and ongoing training of healthcare personnel who insert and maintain catheters [I, A]
- Use of maximal sterile barrier precautions during CVC insertion [I, A]
- Use of >0.5% chlorhexidine skin preparation with alcohol for antisepsis [I, A]
- Avoidance of routine replacement of CVCs as a strategy to prevent infection [I, A]
- Use of antiseptic/antibiotic-impregnated short-term CVCs and chlorhexidine-impregnated sponge dressings, if the rate of infection is not decreasing despite adherence to other strategies [I, A]
- Implementation of bundled strategies, including documenting and reporting rates of compliance of all components of the bundle, as benchmarks for quality assurance and performance improvement [I, A]
- Implementation of appropriate patient education programmes, that include instruction on hand decontamination and the prevention of cross-contamination in patients with stomas [I, A]
- The utilisation of neutral pressure mechanical valve connectors to avoid the risk of infection is recommended [III, C]
- A strong recommendation for the use of antibiotic-coated catheters is not warranted [II, B], although they could be useful in institutions where there are high rates of BSIs

Catheter-related thrombosis—diagnosis

- Doppler ultrasound should be carried out if thrombosis is suspected [III, A] (sensitivity 56%–100%; specificity 94%–100%)
- If normal ultrasound and suspected thrombosis or occlusion, venography or alternative imaging should be carried out (magnetic resonance, computed tomography, gadolinium-enhanced magnetic resonance venography or contrast-enhanced computed tomography) [III, A]

Catheter-related thrombosis —treatment

- Anticoagulation therapy with LMWH is the preferred treatment, as it is more effective in preventing thrombosis and has less risk for bleeding compared with VKA [II, A]
- If the catheter is functional and there are no risks for complications, or severe/rapid progressive symptoms, anticoagulation treatment should be continued for the time length of time the catheter is in use [III, C]
- If the CVC is not necessary or non-functioning, or there is concomitant deep vein thrombosis, sepsis, or if long-term anticoagulation is contraindicated, a short course (3–5 days) of anticoagulation therapy is recommended and then the catheter should be removed [I, A]
- LMWH alone or LMWH followed by warfarin should be used for a minimum of 3–6 months [I, C]
- It is recommended to continue anticoagulation therapy at a prophylactic dose, until the catheter is in place [I, C]
- Thrombolytic (urokinase, streptokinase and alteplase) treatment is not recommended as a first-line therapy, due to a greater risk of thrombosis [I, B]

Continued

Table 5. *Continued*

Catheter-related thrombosis —prevention
• Extensive routine prophylaxis with anticoagulants while balancing potential risks and benefits should be done in specific cases due to inconclusive results from thromboprophylaxis trials in cancer patients • Prophylaxis with thrombolytic agents is not recommended [I, A] • Flushing with 0.9% normal saline is recommended [III, C]

CRBSI, catheter-related blood stream infection; CVC, central venous catheter; BSI, blood stream infection; ALT, antibiotic lock therapy; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; ECG, electrocardiogram; PICC, peripherally inserted central catheter; MRSA, methicillin-resistant Staphylococcus aureus; MIC, minimum inhibitory concentration; AST, antimicrobial susceptibility testing; spp., species; C, candida; GNB, gram-negative bacillus; E, enterococcus; S, streptococcus; TEE, transesophageal echocardiogram; MDR, multi drug resistant.

in 27%–66% of cancer patients when they are screened by venography [106], with only 0.5%–28% of these cases having symptoms [62]. In the last few years, a downward trend of symptomatic CRT has been noted, with a reported average rate of 4%–8%, this is mainly due to improvements in the catheter material used, surgical techniques and catheter maintenance [62].

There are different types of thrombotic complications associated with CVCs. Major complication occurs when the thrombosis, involving the vein in which the catheter is inserted, leads to serious systemic and life-threatening sequelae, such as pulmonary embolism and sepsis. Minor complications include: ball-valve-type clot on the tip of the catheter; lumen obstruction; fibrin sheath along the length of the catheter and superficial thrombophlebitis. These complications are usually associated with local symptoms or may interfere with the infusion or aspiration from the catheter [107].

There are broadly three main causes of CVC occlusions: mechanical, thrombotic and medication/parenteral nutrition-related. Several mechanical causes can lead to a blockage: kink in catheter, tight suture, huber needle dislodge or occlusion, the catheter tip being blocked by the vessel wall and pinch-off syndrome (compression of the catheter, caused by its passage through the narrow angle between the first rib and the lateral portion of the clavicle). The latter complication is more frequent when the sub-clavian vein is used for access. These risks can be reduced if an ultrasound-guided technique is carried out [108]. Inappropriate concentration or inadequate mixture can cause the precipitation of medications in the catheter lumen (low or high pH, calcium phosphate precipitate, lipid emulsion, high-osmolarity and high-protein nutrition formulas) [109]. Furthermore, thrombotic aetiology could be related to fibrin sheath, intraluminal clot, mural or venous thrombosis [110].

risk factors

Potential risk factors for catheter-related thrombosis are listed in Table 2 [106, 111–124].

diagnosis of catheter-induced thrombosis

CVC-related symptoms are often non-specific. Therefore, a clinical diagnosis is possible in only 40%–47% of cases [125]. Frequently in clinical practice, the first signs are: difficulty aspirating or infusing through the lumen of the catheter, and complaints of local pain or a burning sensation during injection. Other common signs are redness, swelling and oedema. Complications are: infections, blockage of the lumen, circulatory obstruction and thromboembolism. Pulmonary embolism at presentation is rare. Although venography is considered the gold standard for the diagnosis of CRT, Doppler ultrasound is usually carried out [III, A], because it is readily available and non-invasive (sensitivity 56%–100%; specificity 94%–100%) [125–127]. In patients with suspected CRT and a normal ultrasound, or suspected central venous occlusion, venography or alternative imaging should be carried out [magnetic resonance imaging, computed tomography (CT), gadolinium-enhanced magnetic resonance venography or contrast-enhanced CT] [III, A] [110].

treatment of catheter-induced thrombosis

When the CVC is no longer necessary, or if long-term anticoagulation is contraindicated, a short course (3–5 days) of anticoagulation therapy is recommended before removing the catheter, in order to avoid clot embolisation [I, A] [110, 128]. The length of therapy after removal of CVCs has not been established with certainty. According to the severity of thrombosis, 3 months of therapy is usually advised, with some authors suggesting even shorter courses [I, C] [128, 129]. Additionally, if symptoms progress or the blood clot extends into the SVC, the CVC should be removed. If the device remains *in situ* and the patient is not at risk of complications, anticoagulation drugs should be administered [III, C] [130]. Anticoagulant therapy with low molecular weight heparin (LMWH) and vitamin K antagonist can be used [128]. Warfarin can cause complications in cancer patients (e.g. interference between warfarin dosage and some chemotherapy drugs, thrombocytopaenia, nutritional status, metastatic liver disease) [62]. LMWH is more effective in preventing thrombotic recurrences [II, A] [131]: LMWH alone or LMWH followed by warfarin therapy should be used for a minimum of 3–6 months [132]. There are no data for the use of new oral anticoagulants, neither for prevention nor for therapy [133]. It is recommended to continue anticoagulation therapy at a prophylactic dose, until the catheter is in place [I, C] [134]. A comparison of the different guidelines recommendations, for the treatment and the prophylaxis of catheter-related thrombosis, are listed in Tables 3 and 4.

Thrombolytic (urokinase, streptokinase and alteplase) treatment is not recommended as a first-line therapy, due to a greater risk of thrombosis [I, B] [128]. If used, urokinase 5000 IE should be administered and dwell within the catheter for 1 h, before it is aspirated. This procedure can be repeated several times. Alternatively, alteplase 2 mg/2 ml can be administered twice (aspiration after 60 min). Additional treatment options are: SVC filter, mechanical thrombectomy, venous angioplasty and surgical decompression.

In summary, published data and clinical experience suggest that:

- catheter-related thrombosis is associated with a low risk for recurrence and post-thrombotic syndrome and, therefore, conservative treatment is recommended,
- removal of the CVC is required in cases of concomitant deep vein thrombosis, sepsis, non-functioning or if central access is not necessary,
- either LMWH alone or LMWH followed by warfarin should be used for a minimum of 3–6 months.

prevention

Extensive, routine prophylaxis with anticoagulants to prevent CRT is not recommended [I, A] [137, 138]. The use of thrombolytic agents (e.g. urokinase) shows inconclusive results in different trials, and there are insufficient data for it to be recommended [139, 140]. New materials, such as ionic implantation of silicone chromic venous access devices and silver-coated CVCs, have not been shown to relevantly affect rates of thrombosis [62]. In critically ill patients, heparin-bonded CVCs have been shown to significantly reduce the incidence of CRT and infection, but data for oncological patients are lacking.

Intermittent flushing with heparin is a standard practice in the maintenance of CVC patency. However, when compared with 0.9% normal saline flushing, no differences in thrombosis rates were found [I, C] [20, 141]. Prevention of catheter occlusion by heparin installation is widely discussed. If used, unfractionated heparin (>500 IE) should be administered.

In cancer patients, thromboprophylaxis with warfarin or LMWH has provided inconclusive results in outpatients. Two large prospective trials, PROTECHT [142] (daily nadroparin) and SAVE-ONCO [143] (daily semuloparin) evaluated the use of LMWH in cancer patients. Despite the fact that thromboprophylaxis appears to be effective, safe and feasible, the event rate was low (PROTECHT: 2% in the treatment group versus 3.9% in the placebo group; SAVE-ONCO: 1.2% in the treatment group versus 3.4% in the placebo group). Therefore, the use of anticoagulant prophylaxis in patients with cancer should be accurately evaluated, balancing potential risks and benefits in every single case [144].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 5. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [145].

conflict of interest

The authors have declared no conflicts of interest.

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