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REVIEW ARTICLE

Recommendations for the use of long-term central venous catheter (CVC) in children with hemato-oncological disorders: management of CVC-related occlusion and CVC-related thrombosis. On behalf of the coagulation defects working group and the supportive therapy working group of the Italian Association of Pediatric Hematology and Oncology (AIEOP)

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Abstract Central venous catheters (CVC), used for the management of children with hemato-oncological disorders, are burdened by a significant incidence of mechanical, infective, or thrombotic complications. These complications favor an increasing risk in prolongation of hospitalization, extra costs of care, and sometimes severe life-threatening events. No guidelines for the management of CVC-related occlusion and CVC-related thrombosis are available for children. To this aim, members of the coagulation defects working group and the supportive therapy working group of the Italian Association of Pediatric Hematology and Oncology (AIEOP) reviewed the pediatric and adult literature to propose the first recommendations for the management of CVC-related occlusion and CVC-related thrombosis in children with hemato-oncological disorders.

Keywords Central venous catheter · Thrombosis · Pediatric hematology oncology · CVC occlusion

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Introduction

Long-term central venous catheters (CVC) have been increasingly used in the last 30 years for the management of children with malignancy. The CVC are fundamental to deliver safely multidrug chemotherapy and intensive support therapy such as antimicrobial agents, analgesics, blood products, hyperhydration, and hyper-osmolar total parenteral nutrition (TPN). CVC can be either tunnelled (single lumen or multilumen) with a subcutaneous cuff adjacent to the catheter exit site (i.e., Broviac Hickman, or Groshong) or a totally implanted port system with a subcutaneous reservoir [1–4]. Despite their undoubted utility, the use of the CVC is burdened by a significant incidence of mechanical, infective, or thrombotic complications, affecting 14–36 % of patients within 2 years from the placement of CVC [5]. CVC represent the most frequent cause of thrombosis in pediatric age [6, 7]. The formation of blood clots within the lumen or the tip of the

CVC often results in a difficulty or impossibility to obtain blood; a more serious complication is represented by deep venous thrombosis (DVT), mainly occurring on the upper venous system [8, 9]; these complications can determine a prolongation of hospital stay, increasing costs of care as well as life-threatening conditions requiring urgent systemic treatment or CVC removal. The prevention and the treatment of CVC-related complications thus play a pivotal role, and specific surveillance programs are crucial both to monitor the risk factors for CVC complications and to improve their management. We reviewed the pediatric and adult literature to propose specific guidelines for the management of CVC-related occlusion and CVC-related thrombosis in children with hemato-oncological diseases.

Methods

The supportive therapy working group of AIEOP promoted the definition of the guidelines for the management of long-term CVC in pediatric hemato-oncological patients. An expert panel defined the topics to discuss and performed a literature search. The keywords used for the selection of the studies regarding CVC-related occlusion and CVC-related thrombosis were "central venous catheter, occlusion, thrombosis, catheter-related thrombosis, children, pediatric malignancy, onco-hematology." The search was limited to English language papers and the period analyzed was from January 2000 to January 2014. The reference list of papers selected by literature was also used as source. The results of the search were discussed and scored by the members of the panel using the scoring system proposed by the Infectious Diseases Society of America (Table 1). The recommendations were proposed and discussed in a second meeting, and the results of this debate were the basis for the final document. The definite document was approved by all members in a third meeting during 2014.

Definitions and diagnosis

Occlusion The occlusion of the CVC may be partial (dysfunction, withdrawal occlusion), when it is possible to infuse solutions in the catheter but not withdraw blood, or complete, when the total flow in the catheter is precluded in both directions [10].

Thrombosis The CVC-related thrombosis is a venous thrombosis which develops along the course of or close to the catheter, not completely obstructing the lumen of the vessel [5]; a CVC-related thrombosis totally blocking the involved vessel is a DVT [5]. The causes of obstruction may be mechanical, chemical (drugs or nutrients, precipitating in the lumen), or thrombotic [4, 5, 11–17]. One of the most frequent causes of CVC dysfunction and occlusion is the formation of a fibrin sheath inside the lumen or at the apex of the catheter, especially in that case without apparent signs of compression or of dislocation, and without a history of infusions of drugs at risk of giving precipitates (i.e., TPN, etoposide, etc.). A randomized study showed that the deposition of a fibrin sheath occurred more frequently when catheter function was maintained through periodical flushes with saline and in case of use of a CVC with a positive pressure valve compared to heparinized solution and a CVC without a positive pressure valve [18]. In case of CVC dysfunction, you should try to solve the occlusion (partial or complete) by infusion of saline, postural changes, behavioral changes of the patient (i.e., to lift arms, to take the supine position, coughing, or Valsalva maneuver) [19]. A lock with urokinase could be an unblocking strategy if the dysfunction persists. In case of failure, you need to perform a chest X-ray, evaluating a possible CVC dislocation, and an ultrasound (US) Doppler searching for a venous thrombosis along the catheter or for a thrombus at the apex [5, 20].

Indeed, two retrospective studies have reported a significant association of CVC dysfunction and TE [9, 12]. Figure 1 summarizes the various thrombotic complications of CVC and the mode of presentation. A CVC dysfunction must always

Table 1 IDSA-United States Public Health Service grading system for ranking recommendations

Quality of evidence	Strength of recommendation
I Evidence from >1 properly randomized, controlled trial	A Good evidence to support a recommendation for use
II Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments	B Moderate evidence to support a recommendation for use
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C Poor evidence to support a recommendation

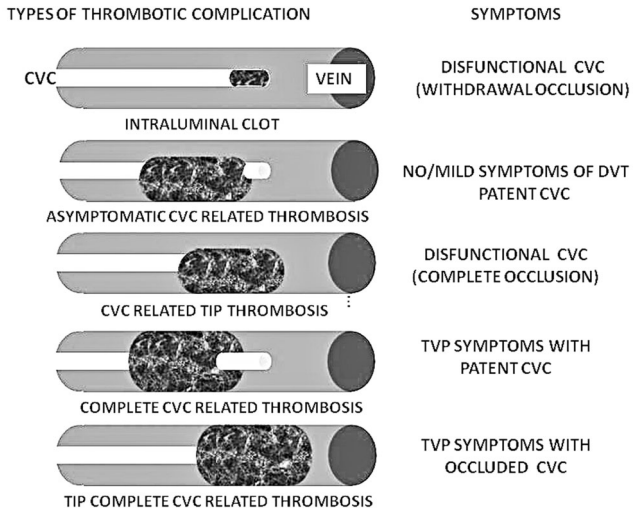

Fig. 1 Symptoms of different types of CVC thrombotic complications

induce suspicion of a venous thrombosis, whose signs and symptoms must be immediately looked for in order to promptly start appropriate treatment. Contrast venography is reported as the gold standard for diagnosis of venous thrombosis, but it is an invasive procedure, involves exposure to ionizing radiation and contrast medium, and is not always available. US is an acceptable alternative, readily available and reliable [21]. In the adult population, US had a reported sensitivity equal to 78–100 % and a specificity of 86–100 % for the diagnosis of DVT of the upper limbs [22–24]. These results are not confirmed in children where the sensitivity of US is reduced to 37 % compared with 79 % of venography, as reported in a study in which US Doppler proved useful for evaluation of the neck vessels but not of thoracic vessels [25, 26]. Other useful methods are computed tomography (CT) and magnetic resonance imaging (MRI) [5, 19, 27, 28]. CT provides a useful three-dimensional reconstruction of thoracic vessels and upper limbs, but exposes patients to radiation and contrast. MRI requires a longer execution time and optimal cooperation of the patient to avoid motion artifacts. In both cases, if the child is aged <6 years, sedation is essential to ensure the proper conduct of the examination.

Recommendations

In case of suspected mechanical dysfunction (as catheter dislocation, apex misplacement, or CVC rupture), a chest radiogram, with or without line infusion of contrast medium, is the first instrumental investigation (IIB).

In case of suspected CVC-related thrombosis or DVT, US Doppler is the first-line diagnostic investigation (IIB).

For the diagnosis of a CVC-related thrombosis, CT or MRI should be performed as a second-line imaging test if US Doppler is not available or the result is unreliable or a false negative is suspected (IIC).

Treatment of CVC occlusion

Treatment of chemical occlusion

The use of sodium hydroxide (NaOH) 0.1 M is suggested to recover the function of the CVC blocked by basic substances as lipids [5, 11], also by continuous infusion lasting up to 15 h [5, 11, 29, 30]. The use of hydrochloric acid (HCl) 0.1 N is an effective solution to solve the blocking of the catheter due to precipitates of calcium phosphate crystals or acidic substances [5, 11, 13, 31, 32]. Recent data show that HCl ≤2 M does not damage silicone CVC [33–35]. The instillation of a solution of ethyl alcohol 70 % in sterile water (up to 3 ml, maximum 0.55 ml/kg) has been proven generally effective for removing occlusions due to lipids [13, 36], although an association with venous thrombosis [37] and the risk of damaging polyurethane CVC [34] have been reported.

Recommendations

The use of NaOH 0.1 M (volume up to 150 % of CVC capacity, left in situ up to 6 h) is indicated for CVC occlusions due to precipitates of basic substances (IIB).

The use of HCl 0.1 N (volume as CVC capacity, left in situ up to 1 h) is indicated for CVC occlusions due to precipitates of calcium phosphate crystals or acidic substances (IIB).

The use of etilic alcohol 70 % in sterile water (up to 3 ml, maximum 0.55 ml/kg) is indicated for CVC occlusions due to lipids, in silicone CVC only. Its use is not recommended in polyurethane CVC for the risk of damaging the catheter structure (IIC).

Treatment of thrombotic occlusion

The first approach to restore catheter patency requires the use of thrombolytic agents with an established role in the management of thrombotic complications of CVC [3, 5, 10, 19]. Several studies have demonstrated the efficacy of recombinant tissue plasminogen activator (rt-PA) for the treatment of occlusive dysfunction of CVC in children. Many studies reported different time exposure and age- and weight-adjusted doses of rt-PA, but it could be concluded that rt-PA is a safe drug for unblocking occluded catheters, with effective doses ranging from 0.1 to 2 mg, at the concentration of 1 mg/ml, instilled into the CVC and left in situ for periods from 20 min to 4 h [5, 20, 38–40].

Urokinase (UK) has been widely used to restore patency of occluded CVC and for the treatment of CVC-related thrombosis [3, 10, 19, 41, 42]. Different dosages have been used both for the intraluminal instillation and for systemic infusions lasting several hours. All the authors reported significant success rates: UK 5,000 IU/ml for 15–60 min was effective in solving the problem in a high percentage (89–98 %) of CVC

placed in pediatric patients [42–44]; a higher dose (25,000 IU) did not show superior efficacy [42]. Some authors demonstrated that continuous infusion of low-dose UK offers a second-line approach in patients with a CVC which is not completely occluded or which displays a small thrombus on the catheter tip [45]. In case of complete occlusion with no evidence of CVC-related thrombosis, systemic infusion of UK for several hours through a peripheral vein showed a significant rate of success in adult patients [46] and in children [42]. Intraluminal or systemic (depending on needs and situations) infusion of UK is an important option to avoid the replacement of the CVC and preventing further thrombotic complications [5].

Recommendations

In case of thrombotic occlusion of CVC, intraluminal instillation of thrombolytic solution at a quantity filling the CVC capacity is recommended: either UK at a dose of 5,000 IU/ml or rt-PA 1 mg/ml, to be left in situ for 15–60 min (IIB).

In case of persistent thrombotic occlusion (total or partial) of CVC, refractory to the previous procedure, and in the absence of CVC-related thrombosis, systemic infusion of UK is indicated, at the dose of 1,000 IU/kg/h for 3 h, to be repeated several times up to a maximum of 12 h, or 200 IU/kg/h up to 24 h (IIB).

CVC-related thrombosis

Early diagnosis and proper treatment are essential to prevent long-term sequelae of CVC-related thrombosis. The post-thrombotic syndrome (PTS), characterized by persistent pain, swelling, and skin changes, is becoming an emerging problem in the pediatric age [21]. Signs and symptoms of PTS have been reported after CVC removal: mild PTS was present in 39 % of children and pain symptoms were reported in 9.5 %; a higher rate of PTS has been reported in children with a history of CVC occlusion [47]. Screening cancer survivors for PTS after CVC removal should be integrated to the after-cancer clinical follow-up. Obstruction of CVC may indicate asymptomatic DVT [47].

General prothrombotic risk factors

Many factors contribute to the pathogenesis of CVC-related DVT: the damage of the vessel wall consequent to CVC insertion, venous stasis/obstruction of venous outflow as a result of the permanence of the CVC, the occlusion of the vessel due to the size of the CVC compared to the relatively small size of the veins of the upper limbs, the irritation of the endothelium by the CVC itself, or the action of infused substances [8, 9]. The damage to the endothelium, releasing procoagulant factors and causing platelet activation, can induce the formation of a thrombus associated with the CVC which can, in turn, cause the occlusion of a deep vein in the limbs [8]. CVC and cancer are independent risk factors for the occurrence of thrombosis [48]. In patients with cancer, the risk of thrombosis is higher because the cancer itself can induce a hypercoagulable state; also thromboses in the upper limbs are more common in cancer patients and in carriers of CVC [8, 49] with reported incidence between 0.3 and 28.3 % [50]. Patients with tumors in the mediastinum and chest are at increased risk of thrombosis due to the direct effect of the mass on the venous flow [8]. Most DVT of the upper limbs associated with CVC are clinically asymptomatic and frequently remain undetected [6–9]; the clinical relevance of asymptomatic CVC-related thromboses is still debated, and screening for this condition is generally not recommended [51].

Specific prothrombotic risk factors

CVC-related infections The risk of CVC-related DVT is higher in adults and pediatric patients with cancer receiving chemotherapy with a history of previous CVC-related infection [7, 52, 53].

Hemato-oncological diseases Children with acute lymphoblastic leukemia (ALL) and lymphoma have a higher incidence and an increased risk of CVC-related thrombosis compared with patients with other malignancies [7, 53]. Particularly, a high percentage of asymptomatic venous thrombotic events, localized in the veins of the upper limbs [54], was found in children with ALL and carriers of a CVC. In the same type of patients, the incidence of symptomatic thromboses—including CVC-related ones—during treatment with steroid/*Escherichia coli*-asparaginase was significantly increased in the presence of CVC, prednisone, *E. coli*-asparaginase, and hereditary thrombophilia; in this group of patients, prophylaxis with low molecular weight heparin (LMWH) reduced the incidence of symptomatic thrombosis [55].

Thrombophilia In children with ALL with at least one prothrombotic risk factor, a significant correlation between venous thrombosis and CVC was found [56]. A positive family history of thrombosis was associated with the risk of occlusion of the CVC but not with the incidence of DVT in pediatric oncology patients [48, 52].

Characteristics of CVC In some studies, the thrombogenicity of the material among different catheters was compared and the incidence of CVC-related thrombosis was significantly greater for polyethylene CVC compared to other materials (silicone, polyurethane, and polyvinyl chloride) [57]. Although a previous correlation was found between the use of external CVC and increased thrombotic risk in children [58], a further study in children with cancer showed no differences in

the risk of thrombosis between an internal or external catheter [59]. No differences in the incidence of thrombotic complications among Hickman-Broviac-type single-lumen or double-lumen catheters and single-lumen catheters with a pressure valve have been reported in pediatric patients with hemato-oncological diseases [14]. A prospective study in children with ALL showed a significant correlation between the median diameter ratio of the CVC (expressed in French)/weight (kg) >0.4 and diameter of the CVC (French)/body surface area (m^2) >9.6 and risk of CVC-related venous thrombosis [27].

CVC dysfunction There is a significant association between the presence of CVC dysfunction and CVC-related thrombosis in children with cancer [7, 59]. The risk of CVC-related DVT seems to be higher in patients with a history of repeated occlusion of the CVC. Patients with a history of CVC-related infection and occlusion of the CVC have a 6.4 times higher risk of having a CVC-related DVT [7, 47, 52].

Method of CVC insertion A lower thrombogenicity resulted from the insertion of the catheter from the right side and from the placement of the distal tip at the junction of the superior vena cava and the right atrium; the femoral location, the prolonged time of the positioning procedure (over 22 min), and the repeated attempts seem to be related with an increased risk of CVC-related thrombosis [60, 61].

Prevention of CVC-related thrombosis

Primary nonpharmacological prevention

Recommendations

To prevent CVC-related thrombosis, use, if possible, the right side for the insertion of the CVC in the upper venous system (IIB).

The distal tip of the CVC must be positioned at the junction of the right atrium and the superior vena cava (IIB). The size of the CVC should be carefully chosen in relation to the anthropometric evaluation and with the patient's body surface (IIC).

Primary pharmacological prophylaxis

The prevention and treatment of venous thrombosis in children are based primarily on anticoagulant drugs and, to a lesser extent, on thrombolytic agents.

The drugs most commonly used are the standard unfractionated heparin (UFH) and LMWH [62]. Refer to specific articles for detailed information on mentioned drugs and their use in pediatrics [63–65].

UFH is a well-known drug, requiring continuous intravenous infusion and frequent monitoring of activated partial thromboplastin time (aPTT); moreover, the evaluation of aPTT is not standardized and, in some situations (such as in neonatal age in which the aPTT may be physiologically elongated compared to the values of the adult), it may be necessary to monitor the effect of UFH by measurement of the inhibition of activated factor X (anti-FXa) (expected value between 0.3 and 0.7 IU/ml). Among the side effects of UFH, the risk of thrombocytopenia induced by heparin (HIT) and, in case of prolonged therapy, of osteoporosis [66] should not be overlooked. For the short half-life (less than 1 h) and easy neutralization by the antidote protamine, UFH remains the drug of choice when a fast neutralization as to perform an invasive procedure or surgical emergency might be necessary. Only one randomized study evaluated the efficacy and safety of UFH (100 IU/kg/day continuous infusion) versus saline in the prevention of CVC-related thrombosis in 108 patients (age 4–60 years) with malignant and non-malignant hematological disease, and the incidence of asymptomatic CVC-related thromboses resulted 1.5 % in patients treated with heparin and 12.6 % in the control group (p=0.03) [67]; given the limited number of patients and the particular clinical specificity (patients undergoing bone marrow transplantation), the authors were unable to provide definitive conclusions on UFH efficacy and safety in the primary prevention of CVC-related thrombosis in cancer patients.

LMWHs can be administered subcutaneously without necessity of monitoring, entail a lower risk of HIT and osteoporosis than UFH, and have less interference with drugs and diet compared to vitamin K antagonists. The LMWHs, unlike the standard heparin, inhibit much more factor X than thrombin (three to eight times) and, generally, do not alter the common screening tests of coagulation (prothrombin time (PT) and aPTT). The tests used to monitor therapy with LMWH (or rather to test if the antithrombotic effect is achieved) is the dosage of anti-FXa; this assay should be performed at least 4–6 h after subcutaneous injection and with the assay method calibrated on the administered LMWH; the therapeutic range varies between 0.5 and 1.2 IU/ml while the prophylactic range varies between 0.2 and 0.4 IU/ml [65]. There are several randomized studies about LMWH for prevention of CVC-related thrombosis in adults, but in three large placebo-controlled studies, the efficacy of LMWH in the prevention of asymptomatic or symptomatic CVC-related thrombosis has not been demonstrated [68–70]. A correlation analysis of five randomized trials of good methodological quality in cancer patients concluded that treatment with LMWH was not effective in preventing symptomatic CVC-related thrombosis but did not increase the bleeding risk [71]. The only randomized pediatric study, PROTEKT, was underpowered and inconclusive but provided useful information on the dosage and safety of reviparin [72]. The recent Cochrane Database Syst Rev [73] found no

significant effects of systemic treatments compared with no intervention in preventing (a)symptomatic venous thromboses in pediatric oncological patients with CVC. One controlled clinical trial, which compared one systemic treatment with another systemic treatment, showed a significant reduction in symptomatic venous thrombosis in patients receiving LMWH in addition to antithrombin supplementation. All studies investigated the prevalence of major and/or minor bleeding episodes, and none found a significant difference between study groups. The LMWH frequently used in children are enoxaparin, dalteparin, and reviparin (respectively 100 IU/kg/12 h, 129± 43 IU/kg/24 h, 100 IU/kg/12 h for the therapeutic dose and 50 IU/kg/12 h, 92±52 IU/kg/24 h, 30 IU/kg/12 h for the prophylactic dose); among them, the most and longer used in children is enoxaparin (1 mg contains 100–120 IU anti-Xa) [66].

On the basis of currently available evidence, authors were not able to give recommendations for clinical practice.

Oral anticoagulants (OA) are burdened with a difficulty of monitoring not only for the need of venous access (which can be partially overcome by measuring prothrombin time through a whole blood coagulometer with capillary samples) but also for dietary reasons and pharmacological interferences. For these reasons, the OA are currently used primarily in long-term prophylaxis. In recent studies, the rate of thrombosis was comparable in oncological patients receiving and not receiving prophylactic treatment with OA [74, 75]; also, a study in cancer patients treated with 5-fluorouracil (FU) showed that the combination of low doses of OA with 5-FU significantly increases the risk of bleeding [76].

The thrombolytic agents (UK and rt-PA) did not find strong evidence in recent pediatric guidelines, also for the substantial risk of cerebral hemorrhage reported as 12 % in preterm infants, 1.2 % in term infants, and 0.4 % in other pediatric ages [77]. Therefore, administration of thrombolytic agents is suggested only in case of extensive thrombosis with severe organ impairment within 2 weeks after the onset or in case of massive pulmonary embolism [21, 66]. A prospective randomized trial compared the efficacy of fortnightly washes with UK 5000 IU/ml versus heparinized solution 100 IU/ml (in volume sufficient to fill the catheter) in preventing the occlusion of partially or totally implanted catheters; patients randomized to receive UK presented a reduction (1.6 times; p=0003) in occlusive events compared to the control group, but unfortunately, the study was discontinued for withdrawal from the market of UK in the USA, and at the time of study discontinuation, the majority of patients had only about 4 months of observation [78]. A prospective non-randomized study investigated the efficacy and safety of thrombolytic agents (UK 10,000 IU per catheter lumen for 4 h once a week) in 15 children with cancer, and the results were compared with those obtained from a series of 15 children treated with thromboprophylaxis; on US Doppler investigation, the rate of asymptomatic thrombosis in the UK-treated group was significantly lower compared with that of the control group and no bleeding complications were reported [79].

Given the limited number of patients, it was not possible to conclude on the efficacy and safety of thrombolytic agents in the primary prevention of CVC-related thrombosis in cancer patients.

Recommendations

The routine thromboprophylaxis with OA, UFH, or thrombolytic agents for the prevention of catheter-related thrombosis is not recommended in children with cancer (IIA).

Thromboprophylaxis with LMWH for the prevention of catheter-related thrombosis should be considered in selected patients at increased risk of thrombosis (as children with ALL or lymphoma treated with prednisone/*E. coli*-asparaginase and inherited thrombophilia or a history of thrombotic events, or in patients with a mediastinal or thoracic mass) (IIB).

Treatment of CVC-related thrombosis and secondary prophylaxis

Few studies evaluated the efficacy and safety of anticoagulants in the treatment of CVC-related thrombosis, comparing drug versus placebo or each other (see also Table 2).

Table 2 Therapy of venous thromboembolism in children

Situation	Characteristics	Attack	Maintenance
Venous thrombosis (first episode)	CVC related	UH or LMWH for 5–10 days	OA or LMWH×3 months then a prophylactic dose of OAT or LMWH for as long as CVC remains in place
Massive venous thrombosis	With organ failure and onset within 14 days	Thrombolytic therapy for 6–72 h combined with UFH or LMWH, to be prolonged for 10 days	OA or LMWH×6 months
Pulmonary embolism	Without circulatory impairment	UFH or LMWH for 5–10 days	OA or LMWH×6 months
	With circulatory impairment	Thrombolytic therapy for 6–72 h combined with UFH or LMWH which may be prolonged for 10 days	OA or LMWH×6 months

Only a prospective randomized trial examined the efficacy and safety of LMWH in the treatment of CVC-related thrombosis. In this study, 46 outpatients (34 with cancer and 16 carriers of CVC) with upper extremities confirmed DVT were treated with dalteparin (200 IU/kg once daily for a minimum of 5 days) followed by warfarin (INR target 2.0–3.0); at 12 weeks, only one recurrence of DVT and one major bleeding were reported [80]. The REVIVE study on children, although undersized, reported a lower efficacy of treatment with warfarin compared to LMWH in cancer patients [72]. Available data show that therapy with LMWH alone for 3 to 6 months is safe and effective for the treatment of DVT and pulmonary embolism in cancer patients [63]. Treatment with UFH, followed (as early as the first day) by OA, is generally recommended for patients with venous thrombosis and kidney failure [63].

The value of thrombolytic therapy in the treatment of CVC-related thrombosis was evaluated in two prospective randomized trials and in one retrospective study, each one with a limited number of patients. In the first small study, only four adults and one child with cancer and CVC-related thrombosis were treated with continuous infusion of rt-PA (0.5 mg/kg every 24 h, preceded by a bolus of 5 mg in adult patients or of 2 mg in the child) and UFH for 4.5 to 7.9 days. The treatment was effective in resolving the obstruction of large vessels in three of five patients, without bleeding; a partial lysis of the thrombus and a moderately severe hemorrhage were observed in the other two patients [81]. The second study involved 18 cancer patients receiving high-dose chemotherapy who developed CVC-related thrombosis; these patients were treated with UK (75,000–150,000 IU/h for 24–96 h) infused into a vein of the upper limb ipsilaterally to the thrombosis. All patients showed a partial or complete resolution of clinical signs and symptoms while nine patients (50 %) showed a partial radiographic response; four patients presented with major bleeding [82]. The third study compared retrospectively the efficacy of different thrombolytic drugs versus LMWH in 57 patients with CVC-related thrombosis. Thirty-two adult patients received a thrombolytic drug [streptokinase (n=16), UK (n=5), rt-PA (n=4), or a combination of streptokinase and UK (n=7)] in agreement with the study protocol. Sixteen patients (50 %) showed recanalization (as assessed by Doppler US) and there were no serious side effects [83]. In the 25 patients who received therapeutic-dose LMWH followed by OA, recanalization was achieved in only 4 % (p=0009). Moreover, recently, Goldenberg et al. proved that the combination of low doses of systemic rt-PA and heparin therapy in the first stage of treatment of an acute thrombotic event significantly reduces the incidence of PTS [84].

In another study, rt-PA at very low doses (0.01 to 0.06 mg/kg/h) has been successfully administered for the treatment of venous thrombosis in children, obtaining vessel recanalization in 12 of the 17 treated children, without bleeding complications [85].

It was hypothesized that the slow infusion of the thrombolytic drug at very low doses increases the contact with the thrombus, reducing the risk of bleeding [21]. This protocol would suit particularly hemato-oncological patients who often have an increased risk of bleeding. In case of choosing systemic thrombolytic therapy, this can be infused slightly retracting the CVC or cannuling an ipsilateral vein so that the drug reaches predominantly the site of the thrombus (Fig. 2) [3, 10, 19].

It is not possible to conclude with certainty about the effectiveness and safety of thrombolytic agents, administered systemically or locally in children with cancer and CVC-related thrombosis. For dosages of thrombolytic therapy, see Table 3.

Anticoagulant or thrombolytic treatment in patients at increased bleeding risk, with thrombocytopenia or hypofibrinogenemia

In children with cancer complicated by thrombocytopenia (due to underlying disease or chemotherapy), it has been suggested to maintain a platelet count of at least 50,000/mm^3 during the first 2 weeks of treatment with LMWH [21, 86]; after this period, a modulation of therapeutic dose of LMWH is recommended in case of thrombocytopenia. For platelet values between 20,000/mm^3 and 50,000/mm^3, it is recommended to halve the dose; treatment should be discontinued in case of more serious thrombocytopenia [86, 87]. In case of hypofibrinogenemia, transfusion therapy has been suggested to keep the fibrinogen level higher than 100 mg/dl [21, 87]. The aforementioned protocol with very low doses of rt-PA [85] should be considered in hemato-oncological patients with thrombocytopenia and/or hypofibrinogenemia, if thrombolysis is needed.

Management of heparin anticoagulation in children with asparaginase-related AT deficiency A decrease in antithrombin (AT) production is a well-known complication of

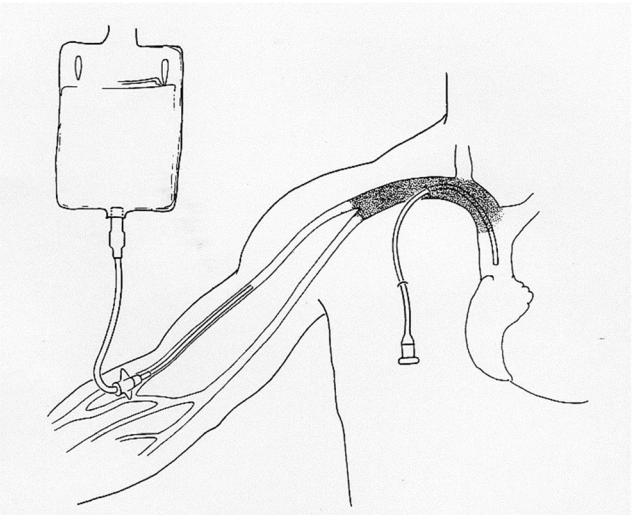

Fig. 2 Management of infusion of systemic thrombolytic therapy

Table 3 Schedule for fibrinolytic therapy

	Urokinase	rt-PA
Attack dose	4400 IU/kg in 5′	Only for PE, 0.1–0.2 mg/kg
Maintenance	4400 IU/kg/h until 72 h	0.1–0.3 mg/kg/h×6 h 0.03–0.06 mg/kg/h×12–96 h
Association	UFH 15–20 IU/kg/h LMWH 1.5 mg/kg	UFH 15–20 IU/kg/h LMWH 1.5 mg/kg/day
In the newborn	Adding FFP 10 ml/kg may be necessary.	
Monitoring and precautions: if fibrinogen is <100 mg/dl, halve the dose or infuse fibrinogen or FFP. Keep the platelet count >50,000/10^9/l.		

PE pulmonary embolism, *FFP* fresh frozen plasma

asparaginase treatment in children with malignancies, and this modification has been related to an increased rate of thromboembolic complication [53]. In the past years, some attempts have been done to demonstrate the utility of substitutive treatment with AT concentrates, but although a positive trend toward a protective effect of AT prophylaxis was found in one study [88], in another one, no clear results were obtained [89]. Consequently, as we would like to give to readers as much as possible evidence-based recommendation, we cannot recommend AT substitution in children with cancer and asparaginase-related AT deficiency . However, AT is the principal heparin cofactor, and low levels of this protein is related to so-called heparin resistance [21]. Prof. Manco Johnson used to replace AT in neonates with very low AT levels candidate for heparin treatment. Although we were not able to find in literature a similar experience in children with asparaginase-related AT deficiency, we do believe that AT concentrate could be used to optimize heparin activity in children with cancer and asparaginase-related AT deficiency, but we are not able to provide a recommendation in this direction.

Evaluation of catheter removal

The available published data are insufficient to conclude on the value of catheter removal. There are no reliable data on the optimal duration of anticoagulant treatment once the CVC is removed because of thrombosis.

Recommendations

The prolonged administration of LMWH (3–6 months) is recommended for the treatment of CVC-related thrombosis (IIB).

Short-term use of LMWH followed by OA can be proposed in case of refusal or impossibility of a prolonged treatment with LMWH (IIB).

Treatment should be based on the use of UFH, followed (as early as the first day) by OA in case of severe renal insufficiency (IIB).

In case of thrombocytopenia due to disease or treatments, after the first 2 weeks of DVT treatment with full-dose LMWH, it is suggested to halve the dose of LMWH if the platelets fall below 50,000/mm^3 and to suspend treatment with a platelet count less than 20,000/mm^3 (IIIC).

The maintenance of the catheter is justified in the case in which the catheter is mandatory for the patient; it is functioning, with the distal tip in the right position; and it is not infected, with a favorable clinical evolution and under close medical supervision; in this case, after the period of anticoagulant therapy at therapeutic dose, prophylactic anticoagulation should be maintained until the catheter is present (IIB).

In case of catheter removal, anticoagulant treatment for 5–10 days is indicated before proceeding with the removal; anticoagulant treatment must be suspended during the removal procedure but resumed immediately after, and continued, considering bleeding and thrombotic risks, for at least 3 months (IIIC).

If insertion of a new catheter is needed, the status of the upper venous system must be evaluated by an ultrasound scan or Doppler (IIIC).

The administration of thrombolytic agents for the treatment of CVC-related thrombosis can be considered only in certain circumstances, where the thrombotic risk is higher than the risk associated with the use of these drugs, namely in case of thrombosis of the superior vena cava associated with a recent, poorly tolerated radiologically confirmed, superior vena cava syndrome or absolute necessity to maintain the CVC (IIIB).

In case of thrombocytopenia and/or a decrease of fibrinogen, the prevention of bleeding complications can be pursued by transfusion therapy maintaining a platelet level over 50,000/mm^3 and fibrinogen above 100 mg/dl (IIIC).

In patients with CVC-related thrombosis, with a high risk of bleeding, the slow infusion (up to 42 h) of an extremely low-dose rt-PA at 0.01–0.06 mg/kg/h may be taken into account (IIIC).

The removal of the CVC is not recommended if all the following conditions are present: (a) the distal tip of the catheter is in the right position (at the junction of the superior vena cava and the right atrium), (b) the catheter is working both on entry and extraction, (c) the catheter is mandatory or of vital importance to the patient, and (d) there is no fever or any signs or symptoms of infectious thrombophlebitis (IIIC).

The removal of the catheter is indicated in the presence of a primary risk factor for thrombosis (catheter too short, dislocation, etc.) (IIIC).

Conclusions

Thrombosis is a growing and significant problem in children with cancer and CVC. Thrombosis can be treated with anticoagulant therapy, so it is important to have reliable methods for early diagnosis. In addition, thrombosis may be preventable

with anticoagulant prophylaxis. Children with cancer are also at risk of bleeding due to thrombocytopenia and other effects of treatment. Ideally, thromboprophylaxis should be offered only to those patients with high risk of thrombosis and low or acceptable risk of bleeding. Further studies are needed to reach a diagnosis of thrombosis as early as possible, and randomized controlled trials of prophylactic anticoagulant therapy in children with cancer are required. This will ultimately help to reduce the incidence of thrombosis and its impact on the overall outcome as well as the quality of life in children undergoing treatment for cancer. Studies comparing the practices of CVC insertion and care across pediatric oncology units and tertiary care centers would be helpful to develop evidenced-based guidelines for CVC insertion and care.

Also studies on long-term sequelae as PTS are needed; whether thromboprophylaxis and/or prevention of CVC occlusion could decrease the rate of PTS needs to be clarified. Screening cancer survivors for PTS after CVC removal should be integrated to the after-cancer follow-up clinical assessment.

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Conflict of interest The authors declare that they have no conflict of interest.

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