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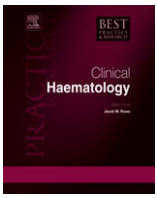

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Thrombosis in childhood acute lymphoblastic leukaemia: epidemiology, aetiology, diagnosis, prevention and treatment

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Acute lymphoblastic leukaemia (ALL) is the most common malignancy associated with venous thromboembolism (VTE) in children. The prevalence of symptomatic VTE ranges from 0% to 36%, and the variation can be explained, at least in part, by differences in chemotherapeutic protocols. The mechanism for increased risk of VTE is associated with alterations in the haemostatic system by use of L-asparaginase (ASP) alone or in combination with vincristine or prednisone, presence of central venous lines (CVLs) and/or inherited thrombophilia. The children at greatest risk are generally those receiving *Escherichia coli* ASP concomitant with prednisone. The majority of symptomatic VTEs occur in the central nervous system or in the upper venous system. In the majority of cases, asymptomatic VTEs are associated with CVLs. External CVLs are affected more often than internal CVLs. Evidence-based guidelines on prevention and treatment guidelines for ALL-related VTE are lacking, and carefully designed clinical trials are needed urgently.

Over the last 20 years, venous thromboembolism (VTE) has been increasingly recognized as a important clinical entity in children [1,2]. VTE in children is associated with mortality and significant morbidity, including lack of thrombus resolution in 50% of cases, risk of recurrence, loss of venous access and development of post-thrombotic syndrome [3–5]. In children, VTE is usually a secondary

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complication of life-threatening primary underlying medical disorders and/or therapeutic interventions for these disorders including central venous lines (CVLs) or chemotherapy [1,2,5]. Cancer is one of the most common primary disorders in paediatric VTE, accounting for one-fifth of children with thrombotic events [1,6]. Acute lymphoblastic leukaemia (ALL) is the most common type of cancer diagnosed in children, and has been reported as the most common malignancy associated with VTE in the paediatric age group [7–10]. Therefore, the objective of this chapter was to review current knowledge on the epidemiology, aetiology, diagnosis, prevention and treatment of VTE associated with paediatric ALL.

Methods

The present review was based on searches of EMBASE, Medline and PubMed, including literature published in any language since 1970 on ALL, malignancy and VTE, central-line-associated VTE, stroke or any alteration of the haemostatic system in neonates, infants and children.

Prevalence of VTE in children with all

The reported prevalence of VTE in children with ALL ranges between 1% and 73% [11–46a]. Variations in the reported prevalence can be explained by differences in VTE diagnostic methods, study design and chemotherapy protocols. Prospective studies including only clinically symptomatic VTE report prevalences between 3% and 14%. A recent meta-analysis of prospective studies in children with ALL found that the overall risk of symptomatic thrombosis was 5.2% [95% confidence interval (CI) 4.2–6.4] [9,20,23,43,47]. Studies that used radiographic tests to screen for asymptomatic deep vein thrombosis (DVT) report prevalences of 37–73% [16,26,48,49]. However, the clinical significance of radiographically detected, asymptomatic DVT is controversial. A very recent study has shown that in survivors of childhood ALL who were diagnosed with asymptomatic VTE during chemotherapy, 50% had post-thrombotic syndrome; a prevalence comparable with that of symptomatic VTE in children [4,50]. A diagnosis of VTE is usually based on the clinical suspicion of VTE due to symptoms such as swelling, erythema, skin discolouration, increased warmth, pain, tenderness, venous distension, presence of subcutaneous collateral veins or loss of CVL patency. It is well recognized that a clinical diagnosis of thrombosis is both insensitive and non-specific [51]. Therefore, in children with asymptomatic thrombosis, major destruction of the venous system can occur which results in loss of venous access, risk of sepsis and a lifelong increased risk of recurrence. In addition, a real risk for pulmonary embolism occurs in the presence of asymptomatic thrombosis.

Age at onset

The typical age distribution of paediatric VTE is shown in Fig. 1. Whereas in the general paediatric population, the first VTE peak is found in the neonatal period and during the first year of life, in children receiving chemotherapy for ALL, the occurrence of symptomatic VTE is described mainly in children $>$12 months of age with a trend towards older children [7,9].

Imaging methods

Duplex sonography, venography, computed tomography (CT) and magnetic resonance (MR) imaging are used to diagnose VTE in children with ALL. Ultrasound has been shown to be sensitive for detection of VTE in the jugular veins but insensitive in the central venous system, whereas venography is sensitive in the central venous system and insensitive in the jugular veins [52]. Therefore, for suspected thrombosis in the upper venous system, patients can be screened using Doppler ultrasound, but if negative, bilateral venography needs to be performed to complete the diagnosis [52,53]. CT/MR imaging and MR angiography/conventional angiography (selected cases only) are recommended to confirm a diagnosis of thromboembolic ischaemic stroke, and MR venography is the method of choice to diagnose cerebral venous thromboses [54]. Ventilation/perfusion scans or MR angiography are suitable methods for diagnosing pulmonary embolism in children.

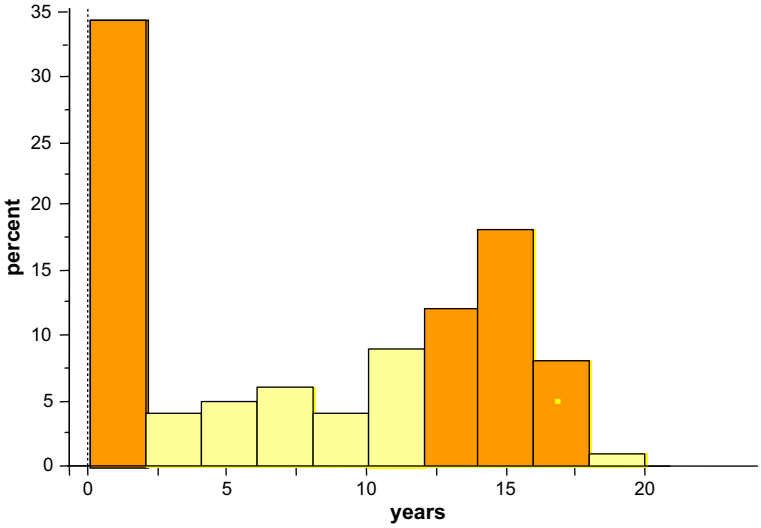

Fig. 1. Age distribution of onset of symptomatic venous thromboembolism in children.

Thrombotic locations in children with all

The majority of thrombotic events are of venous origin, although there are reports of arterial events [26,44,55–58]. A recent meta-analysis of prospective studies in children with ALL and VTE found that symptomatic VTE was diagnosed in the central nervous system (CNS) in 50% of cases, venous VTE in 31% and cerebral infarction or stroke in 18% [9]. In addition, significant rates of CVL-associated thrombosis primarily occurring in the upper venous system have been reported [9,26,57]. Other locations include VTE of the lower limbs (7.7%), pulmonary embolism or right atrium (1%), and superficial VTE (2.2%) (Fig. 2; modified according to Reference [9]). Publications including asymptomatic cases report the majority of events (96.6%) in the upper venous system, with only 3.4% of events within the CNS [16,26,57]. Right atrial thromboses occur in 2% of patients with symptomatic thrombosis, but are more common in studies where patients are evaluated for both symptomatic and asymptomatic events with a prevalence rate of 13.6% in the Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase (PARKAA) study [26,57].

Central venous lines

Use of CVLs has become standard practice to maintain venous access in children with ALL, facilitating the administration of chemotherapy, blood products and other intravenous therapy, and also allowing repeated blood drawing. CVLs inserted as internal (subcutaneous port-a-cath) or external lines (Broviac/Hickman catheter) have improved the quality of care and quality of life in children with ALL. However, CVLs are associated with significant morbidity, such as infection or VTE. The association of CVLs with VTE in children is well recognized; children with ALL are more likely to have CVL-related thromboses than children with other malignancies [1,7]. The majority of CVL-related VTEs are asymptomatic and most frequently located at the entry site of the catheter into the vein [16,26,57]. CVL-related VTE can also lead to recurrent VTE (4–19%), pulmonary embolism (8–15%), post-thrombotic syndrome (5–25%) and death (2–4%) [5,50,59].

In a retrospective analysis of patients with standard risk ALL, McLean et al demonstrated that external CVLs were associated with an increased risk of thrombosis compared with internal CVLs and were more likely to be removed. Interestingly, the authors demonstrated that CVL placement prior to

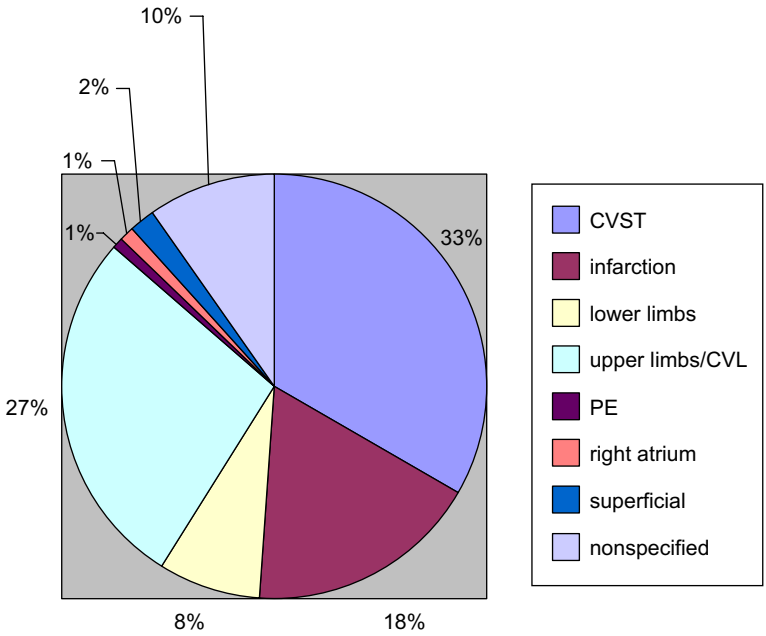

Fig. 2. Distribution of locations of symptomatic venous thromboembolisms in children receiving chemotherapy for acute lymphoblastic leukaemia (modified from Reference [9]). CVST, cerebral venous sinus thrombosis; CVL, central venous line; PE, pulmonary embolism.

Day 15 of induction was associated with increased risk of infection, but this was not a risk factor for VTE or CVL removal [60].

Role of inherited prothrombotic defects

Inherited thrombophilia has been shown to be associated with increased risk of thrombosis in specific patient populations. Determining markers that identify patients at increased risk could potentially lead to targeting high-risk populations for clinical trials of primary or secondary prevention. In general paediatric populations with symptomatic VTE associated with underlying medical diseases, a recent meta-analysis has shown that the presence of inherited thrombophilic traits is associated with increased risk of VTE onset and recurrence [61]. In paediatric ALL, there are conflicting reports in the literature on the relationship between inherited thrombophilia and increased VTE risk [16,23,26,34,62–65]. One study found that thrombophilic markers were associated with the severity rather than the prevalence of VTE [16]. The largest study to date is a multicentre, prospective German study that evaluated the risk of thromboembolism in children who had at least one identifiable prothrombotic defect at diagnosis. This study found that protein C, protein S and antithrombin (AT) deficiency were associated with the greatest risk of VTE [34]. The German study found that the risk of developing symptomatic VTE was greater in patients with inherited thrombophilia (46.5% vs 2.2%, $P < 0.0001$); patients with multiple defects had a significantly higher risk compared with those with a single defect ($P = 0.009$). In contrast, the North American PARKAA study failed to show any correlation between the presence of the factor II 20210A variant or the FV G1691A mutation and development of asymptomatic VTE [26]. In this study, patient numbers were small and the study may have been underpowered to detect a statistically significant association. The majority of VTEs were asymptomatic and there is a possibility that asymptomatic VTE may be associated to a lesser degree with inherited thrombophilia, although the biological rationale for this explanation remains elusive. In a recent meta-analysis with data from five prospective studies, Caruso et al

demonstrated that inherited thrombophilia increased the risk of VTE in ALL patients by approximately 8.5 (4.4–17.4) [9]. However, the authors note that the discrepancies in findings between the studies indicate that the results should be interpreted with caution, as more prospective studies are needed.

Role of chemotherapy in children with all and VTE

The importance of treatment in the pathogenesis of ALL-related VTE is indicated by the observation that VTE rarely occurs at diagnosis and occurs almost exclusively on treatment [7–9]. Approximately 90% of cases occur during induction, and the remaining 10% occur during consolidation or therapy intensification protocols (Table 1). Therefore, research has focused on chemotherapeutic agents administered and their influence on haemostasis. Alterations in haemostasis have been well documented in children receiving L-asparaginase (ASP) as a single agent or in combination with vincristine or prednisone, and/or an anthracycline [45,56,66–72]. In fact, when thrombosis occurs in the consolidation phase, the chemotherapeutic protocols call for ASP to be administered [25,56].

Escherichia coli ASP and *Erwinia chrysanthemi* ASP provide highly effective specific metabolic therapy for ALL and non-Hodgkin's lymphoma [73]. ASP catalyses the conversion of the amino acid asparagine to aspartic acid and ammonia, leading to rapid depletion of the circulating pool of asparagine, resulting in decreased protein synthesis in the liver [73]. In humans, the circulating half-lives of asparaginase enzymes from *E. coli* and *E. chrysanthemi* vary widely [74,75]. Moreover, half-lives differ not only between type A and type B strains of *E. coli*, but also between different commercial *E. coli* preparations [76]. One of the most obvious distinctions between *E. coli* ASP preparations is the absence of cysteine in Kyowa ASP, which also has a lower isoelectric point, a lower clearance and a longer half-life than the Bayer type A ASP (Crasnitin). The lower clearance of the Kyowa preparation compared with type A ASP and *Erwinia* ASP results in higher trough levels of ASP activity and prolonged duration of asparagine depletion. This possibly induces prolonged inhibition of protein synthesis as well as undesired effects on other amino acids and proteins, with a higher rate of adverse events on equivalent dosages of *E. coli* ASP. Furthermore, at equivalent

Table 1
Selected references of children with acute lymphoblastic leukaemia receiving known sources of L-asparaginase (ASP) concomitant with steroids without antithrombin or heparin prophylaxis.

Author [ref]	Study design	ASP source	ASP dosage IU/m^2 (duration)	Combination	Protocol	Number of patients with VTE (%)
Zaunschirn [46a]	Prospective	*Erwinia* i.m.	5000/day (21×)	VCR/Pred/DNR	Induction	0/13
Legnani [22]	Prospective	*E. coli* A i.m.	3 × 6000/week (9×)	VCR/Pred	Induction	0/12
O' Meara [46b]	Prospective	*Erwinia* i.m.	5000/day (21×)	VCR/Pred/DNR	Induction	0/12
Semeraro [42]	Prospective	*E. coli* A i.m.	3 × 6000/week (9×)	VCR/Pred	Induction	0/10
Sutor [44]	Retrospective	*E. coli* B i.v.	3 × 10 000/week (8×)	VRC/Pred/DNR	Induction	0/14
Risseeuw-Appel [41]	Prospective randomized	*E. coli* A i.v. *Erwinia* i.v.	3 × 10 000/week (8×)	VCR/Pred/DNR	Induction	0/10 0/10
Pui [91]	Retrospective	*E. coli* Merk i.v.	2–3 × 10 000/week (4–9)	VCR/Pred	Induction	11/460 (18.3)
Miniero [24]	Prospective	*E. coli* A i.m.	3 × 6000/week (9×)	VCR/Pred	Induction	3/53 (5.7)
Mitchell [56]	Prospective	*E. coli* B i.v.	25 000/week (3×)	VCR/Pred/MP	Re-induction	3/30 (10)
Nowak-Göttl [28]	Prospective	*E. coli* B i.v.	3 × 10 000/week (8×)	VCR/Pred/DNR	Induction	5/46 (10.9)
Nowak-Göttl [34]	Prospective	*E. coli* B i.v.	3 × 5000/week (8×)	VCR/Pred[b]/DNR	Induction	27/289 (9.3)
Nowak-Göttl [63]	Prospective	*E. coli* B i.v.	3 × 5000/week (8×)	VCR/Dexa[b]/DNR	Induction	1/56 (1.8)
Athale [92]	Prospective	*E. coli* B i.v.	25 000/week (3×)	VCR/Pred[a]/MP VCR/Dexa[a]/MP HR: plus DOX	Re-induction	6/74 (8.1) 4/17 (23.5) (SR $n = 1$; HR $n = 9$)

VTE, venous thromboembolism; Dexa, dexamethasone; *E. coli* A, Crasnitin (Bayer); *E. coli* B, ASP derived from Kyowa Hacco, Kyogo, Japan; DNR, daunorubicine; DOX, doxorubicine; i.m., intramuscular; i.v., intravenous; VCR, vincristine; Pred, prednisone; SR, standard risk; HR, high risk.

[a] In HR patients, the steroid dose was three times higher compared with SR patients: Pred 120 mg/m^2; Dexa 18 mg/m^2.

[b] Pred dosage 60 mg/m^2; Dexa dosage 10 mg/m^2.

dosage, Erwinase produces significantly lower serum asparaginase activity and asparaginase depletion than *E. coli* ASP, possibly explaining the less pronounced effect of Erwinase on coagulation observed in some studies [77].

Corticosteroid therapy is an important component of ALL treatment and is frequently given concurrently with ASP for remission induction. Corticosteroids have a number of inhibitory effects during inflammatory reactions. In comparison, dexamethasone has a more significant glucocorticoid effect than prednisone, which may explain a more protective role of dexamethasone with respect to VTE development. When comparing the concomitant use of corticosteroids with *E. coli* ASP in ALL treatment, the produced prothrombotic state, e.g. elevation of procoagulant factors and reduction of fibrinolytic potential, is more pronounced when prednisone is administered instead of dexamethasone [31,63]. Although no randomized studies have compared the haemostatic effects and VTE risk associated with different glucocorticosteroids, a historical comparison was published of two Berlin-Frankfurt-Munich (BFM) studies, which showed that the VTE risk during induction was much lower with dexamethasone compared with prednisone (BFM 2000 – dexamethasone = 1.8%, BFM 90/95 prednisone = 10.4%, $P = 0.028$) [63]. The recently published meta-analysis by Caruso et al did not demonstrate a statistically significant difference in VTE prevalence according to the corticosteroid type used in induction; a finding that may be related to a lack of power. However, there was evidence that prednisone was associated with increased risk of VTE in ALL children in post-induction phases (12.2% vs 1.6%, $P = 0.001$) [9].

Multifactorial aetiology of VTE in children with all

In their 2007 review, Payne and Vora pointed out that a relatively low thrombotic risk associated with individual drugs or an inherited defect is amplified in combination with each other or with further risk factors, such as T-immunophenotye, CVLs or inherited thrombophilia [10,16,78,79]. When ASP and corticosteroids are used separately, the risk of thrombosis is low, but when used in combination, the risk increases 8- to 10-fold [8,9,34,41]. The latter was demonstrated by data from a non-concurrent controlled study comparing the risk of symptomatic thrombosis in German children on the Cooperative Acute Lymphoblastic Leukaemia (COALL) 92/97 protocols (1.5%) and those treated on BFM 90/95 (11%) [23,34]. A multicentre prospective cohort study of 420 patients (BFM $n = 300$, COALL $n = 120$) subsequently confirmed these results (BFM = 11.6%, COALL = 2.5%, odds ratio = 7.7, $P = 0.005$) [47]. In both protocols, symptomatic VTE episodes occurred exclusively during *E. coli* ASP exposure, but the difference in incidence was due to the timing of exposure. In these cohort studies, *E. coli* ASP was administered from early induction, concurrent with corticosteroids, i.e. prednisone, in BFM protocols, whereas in the COALL cohort, ASP was administered during consolidation therapy when patients were not receiving prednisone in parallel [14,19,23,28,31,32,34,44,47]. These findings are in keeping with data from the Dana Farber protocol, whereby ASP was administered during consolidation and occurrence of VTE was restricted to the consolidation phase [25]. Another BFM study indicated that the prevalence of VTE was lower when dexamethasone was given in combination with *E. coli* ASP compared with prednisone [63]. Protocol/treatment differences also have an impact on the risk of VTE associated with inherited thrombophilia [23,47]. Although the overall prevalence of prothrombotic defects was no different in the populations at risk (BFM vs COALL), patients with symptomatic VTE had a greater association between VTE and thrombophilia in the BFM cohort than the COALL cohort [47]. For the combined population, only concurrent administration of *E. coli* ASP and prednisone in children with a prothrombotic risk factor was found to increase the risk of a thrombotic event (odds ratio 34.5, 95%CI 4.39–271.42, $P = 0{\cdot}0008$) [47].

Management of VTE risk in childhood all

Given the well-described burden of VTE complications, primary prophylaxis is warranted during ASP exposure [5,50,80–82]. However, at the present time, there have been no adequately powered studies to determine the safety and efficacy of primary prophylaxis in this clinical setting. Therefore, there are no evidence-based data that either factor replacement therapy or anticoagulation reduces the

risk of VTE. In addition, there is insufficient evidence on the safety and efficacy of anticoagulant prophylaxis to justify their routine use outside of studies.

Maintaining CVL patency

Maintaining CVL patency is critical for management of these patients and also as a first step for prevention of VTE. A meta-analysis has indicated that standard unfractionated heparin (UFH) is more effective than placebo (saline) in maintaining catheter patency, thereby reducing the risk for bacterial colonization or infection in CVLs [83]. Furthermore, in a randomized study, Dillon et al demonstrated the beneficial effect of urokinase blocking every 2 weeks; the latter procedure significantly reduced the rate of occlusive events in internal CVLs and the rate of infections in external catheters compared with standard UFH [84]. However, urokinase was removed from the market by the US Food and Drug Administration due to concerns over production procedures. Although urokinase has been re-introduced, the practice of flushing with urokinase has not been implemented into practice in Europe or North America.

Natural anticoagulant replacement therapy

One plausible mechanism for ASP-associated VTE is the reported reduction in natural inhibitors of coagulation, particularly AT. AT is decreased more than any other haemostatic protein during ASP treatment [25,26,56]. Several studies have assessed replacement therapy, either in the form of fresh frozen plasma (FFP) or AT concentrates during ASP exposure [57,85–87]. It is clear that FFP is ineffective in correcting the coagulant deficiencies or normalizing markers of endogenous thrombin generation in children with ALL receiving ASP [57,85,86]. The clinical benefit of AT supplementation in the prevention of VTE has to be determined in future studies. The PARKAA study evaluated the safety and efficacy of AT concentrate in children undergoing ALL therapy with ASP [57]. Results of this open randomized study showed a trend towards a protective effect of AT concentrate but did not achieve statistical significance, mainly because the study was, by design, an underpowered pilot study. Available data do not support the routine use of AT substitution outside of studies in children receiving ASP. Fibrinogen therapy, applied routinely in some centres during ASP treatment, may increase the risk of VTE.

Use of preventive anticoagulation

In a non-randomized ALL cohort, 41 children received the low-molecular-weight heparin (LMWH) enoxaparin; no symptomatic VTE events or bleeding episodes were reported [62]. A recent randomized clinical trial of low-dose warfarin in 62 children with malignancy and a jugular CVL showed no benefit of treatment [88]. Furthermore, in 2008, Meister et al published a prospective cohort study of LMWH and AT ($n = 41$) in comparison with a historical control cohort treated with AT alone ($n = 71$) for primary prevention in children treated according to BFM protocols [89]. Of all patients in the AT group, only 12.7% developed symptomatic VTE (95%CI 6.0–22.7%) compared with 0% in the combined administration group (95%CI 0–8.6%). The authors did not observe major haemorrhage in the patients investigated.

Treatment of VTE in children with all

Although there are no evidence-based studies for treatment of VTE in children with haematological malignancies, LMWH is widely used as the preferred anticoagulant agent [9,10]. In the general paediatric population with VTE, the American College of Chest Physicians (ACCP) guidelines recommend 3 months of anticoagulation for children beyond the neonatal period, with secondary thrombosis extending to 6 months if full recanalization is not seen on follow-up CT or MR venography scan [90]. The recommendation further suggests that in children who have ongoing, reversible risk factors such as treatment with ASP, the anticoagulant therapy should be continued in either therapeutic or prophylactic doses until the risk factor has resolved. For management of children with VTE, the present authors agree and support the ACCP recommendations as suggested by Payne and Vora that VTE should be managed with LMWH over a 1–3-month period [10]. Initially, LMWH should be administered twice

daily to maintain a 4-h post-dose anti-Xa level of 0.5–0.8 (1.0) IU/mL followed by prophylactic doses, e.g. once daily 1 mg/kg up to 50 kg body weight to maintain a 4-h post-dose anti-Xa level of 0.1–0.3 IU/mL during ASP therapy. Children weighing over 50 kg should be treated according to adult guidelines. In the event of symptomatic VTE recurrence on prophylactic anticoagulation, treatment doses are recommended until CVL removal. Furthermore, re-exposure to ASP should be accompanied with once-daily prophylactic LMWH administration starting the day before the first dose and for 48 h after the last dose [10]. Anticoagulation in patients with severe thrombocytopenia requires careful management to avoid serious bleeding complications and to prevent rethrombosis when platelets are increasing either via bone marrow regeneration or due to platelet transfusion. Apart from platelet transfusions to maintain a platelet count of at least $20–40 \times 10^9$/L, a reduction/cessation of LMWH during periods of thrombocytopenia is optional. In case of scheduled lumbar puncture, LMWH should be stopped 24 h before the intervention.

Summary

In children, ALL has been reported as the most common malignancy associated with VTE. The prevalence of symptomatic VTE is dependent on the treatment protocol, and ranges from 0% to 36%. The aetiologies are likely related to alterations in the haemostatic system documented in children receiving ASP alone or in combination with vincristine or prednisone, sometimes complemented by an anthracycline, inherited thrombophilia, and the presence of CVLs. The greatest risk is reported in children receiving *E. coli* ASP concomitant with prednisone. The majority of symptomatic VTEs occur in the CNS or are CVL-related in the upper venous system. The majority of symptomatic cases are associated with CVLs, with external CVLs affected more often than internal CVLs. Evidence-based prevention and treatment guidelines for ALL-related VTE are lacking. On an individual patient basis, preventive measures include maintaining CVL patency, and primary anticoagulation (LMWH) or antithrombin substitution in selected cases. Individual treatment of symptomatic VTE is performed according to the updated ACCP guidelines. There is a need for randomized controlled trials on prevention and treatment of VTE in these children.

Practice points

- the rate of symptomatic VTE is at least 5% of children with ALL
- the rate of asymptomatic VTE rate is between 30% and 70% of children with ALL
- need to use bilateral venography in combination with Doppler ultrasound to diagnose VTE in the upper venous system
- need to perform MR venography to diagnose cerebral venous thrombosis
- up to 50% of symptomatic VTEs are located in the CNS
- up to 30% of symptomatic VTEs are associated with CVLs
- when VTEs are screened for using radiographic tests, the prevalence of CVL-related VTEs is greater than in the CNS
- CVLs increase VTE risk, especially in children treated for ALL
- external CVLs are associated with increased risk of VTE compared with internal CVLs
- inherited thrombophilia may increase the risk of symptomatic VTE in ALL children
- at equivalent doses, *E. coli* ASP type B may have more adverse side-effects compared with *E. coli* ASP type A or *Erwinia* ASP
- in standard risk patients, prednisone may increase VTE risk compared with dexamethasone
- ASP or corticosteroids administered separately have relatively low risk for VTE
- a combination of *E. coli* ASP and prednisone administered in either induction or consolidation chemotherapy have an increased risk for VTE
- children with one or more inherited prothrombotic risk factors receiving a combination of *E. coli* ASP and prednisone may be at the greatest risk for symptomatic VTE

- there is a need for carefully designed randomized trials to determine the safety and efficacy of primary prophylaxis in children with ALL undergoing treatment with ASP
- identifying the children at increased risk within the patient population would optimize the impact of the intervention
- maintaining CVL patency is important, and flushing with UFH is recommended
- further randomized sufficiently powered trials are recommended to clarify the role of any natural anticoagulant replacement therapy
- use of LMWH may be safe in paediatric patients with ALL
- there is a need for randomized controlled trials for VTE treatment in children with ALL
- treatment should be tailored on an individual patient basis using the ACCP guidelines

Research agenda

- Randomized trial with LMWH or new antithrombotic drugs

Conflict of interest statement

None.

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