Thrombotic Disorders

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Contents

Abstract

Thromboembolism is a well-recognized complication of cancer in children, with important clinical and therapeutic implications. The exact incidence is unknown, with wide variation in reported rates. Thromboembolism has been most extensively studied in acute lymphoblastic leukemia but also affects children with other malignancies. Risk factors include the presence or dysfunction of a central venous catheter, inherited thrombophilia, use of asparaginase and steroids, older age, and intrathoracic or metastatic disease. The most commonly affected sites are the central nervous system in acute lymphoblastic leukemia and the upper extremity veins which are often associated with a central venous catheter. Current evidence does not support screening asymptomatic patients or providing routine prophylactic anticoagulation in pediatric cancer patients. For patients with symptomatic thromboembolism, a review of the evidence for different therapeutic anticoagulation modalities is discussed with graded recommendations; due to a lack of reported data, much of the guidelines are based on expert opinion or consensus statements. The necessary duration of therapy is unknown but generally depends on clinical response and the presence of ongoing risk factors for bleeding or thrombosis. Additional research is needed to better understand the epidemiology of thrombosis in childhood cancer and to optimize both therapy and prevention.

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8.1 Introduction

Thrombosis is a well-recognized complication of cancer and its treatment in both adults and children. The etiology of thrombosis in cancer is complex and multifactorial but generally involves all three elements of Virchow's triad: venous stasis, hypercoagulability and endothelial damage. Malignant cells may alter hemostasis by producing inflammatory cytokines and procoagulant molecules. Humoral coagulation abnormalities are common in cancer patients including increased fibrin formation and degradation as well as altered (i.e., increased or decreased) levels of fibrinogen and other clotting factors. Tumor cells may express tissue factor and cancer procoagulants on their surface, upregulate plasminogen activation inhibitor-1 (PAI-1), and secrete prostaglandins and thromboxanes which promote platelet activation and aggregation (Dipasco et al. 2012). Thrombin generation is also increased in patients with acute lymphoblastic leukemia (ALL) at diagnosis and early in treatment (Athale and Chan 2003b). Vascular endothelium may be activated or damaged through complex interactions with tumor cells and leukocytes, as well as by surgical interventions and indwelling central venous catheters (CVCs). The result of these pathophysiologic changes is essentially an acquired thrombophilia, similar to chronic low-grade disseminated intravascular coagulation (Dipasco et al. 2011).

Adults with cancer have a four- to sixfold increase in the risk of thromboembolism (TE), the second most common proximate cause of death in this patient population (Athale et al. 2007; Dipasco et al. 2011). Thrombosis in childhood is much less common than in adults among the general population, with an estimated prevalence of 0.6–1.1 per 10,000 in the United States (Boulet et al. 2011). Over 70 % of TE in children occurs in the setting of chronic disease, including cancer (Kerlin 2012). Malignancy accounts for 25–40 % of all pediatric thromboses, and children with cancer are at least 600 times more likely to develop TE than healthy children (Athale et al. 2008b).

Relatively little is known about the epidemiology of thrombosis in pediatric oncology. The majority of data derive from children with ALL, with a paucity of information regarding other malignancies. In a retrospective study of 726 patients consecutively diagnosed with cancer at McMaster Children's Hospital from 1990 to 2006, 57 patients were diagnosed with TE for an overall prevalence of 7.9 % (Athale et al. 2008b). In this study, the prevalence of thrombosis varied by underlying malignancy: 14.2 % in ALL, 13.2 % in sarcoma, 11.9 % in lymphoma, 5.9 % in acute myeloid leukemia (AML), 2.4 % in Wilms tumor, 2.3 % in neuroblastoma and 0.5 % in central nervous system (CNS) tumors. For all non-CNS malignancies, the overall prevalence of TE was 10.7 %. Significant reported risk factors for TE in children with cancer include the presence of a CVC, older age, treatment with asparaginase or corticosteroids, the presence of metastases, CVC dysfunction, blood vessel compression by a bulky solid tumor, particularly with intrathoracic disease, and in some studies, inherited thrombophilia (Nowak-Göttl et al. 1999; Nowak-Göttl et al. 2003; Athale et al. 2005; Caruso et al. 2006; Paz-Priel et al. 2007; Athale et al. 2008). Clinical manifestations are similar to those of TE in children without malignancy and vary with the location and extent of thrombosis. The risk of recurrent TE in childhood cancer is not known, but recurrence rate of TE in children generally is estimated to be 5–10 % and may be higher for those with ongoing risk factors such as a CVC, malignancy and asparaginase treatment (Kerlin 2012). The impact of thrombosis on morbidity, mortality, and outcome in childhood cancer is unknown, and management recommendations are generally extrapolated from the adult literature; graded guidelines based on reported evidence are presented in Table 8.1.

8.2 Acute Lymphoblastic Leukemia (ALL)

The incidence of thromboembolism in children with ALL is estimated to be between 1.1 and 36.7 % (Athale and Chan 2003a). This wide

variation is likely due to differences in the definition of TE (symptomatic versus occult), diagnostic methods, study design, reporting period and treatment regimens. The true incidence is likely underestimated because patients are generally not screened for asymptomatic TE. The Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase (PARKAA) study reported a TE incidence of 36.7 % with prospective screening radiography after induction therapy; only 5 % were clinically symptomatic (Mitchell et al. 2003b). A meta-analysis estimated the rate of symptomatic thrombosis in 1,752 children with ALL from 17 prospective studies to be 5.2 % (Caruso et al. 2006). The risk is highest during induction, with an incidence rate more than double that in later phases of therapy. Although rare, thrombosis can also occur prior to the start of ALL treatment (Payne and Vora 2007).

The CNS is by far the most common location of thrombosis in ALL, accounting for 54 % of events in the meta-analysis by Caruso et al. (2006). Twenty-nine percent of these were cerebral sinovenous thromboses (CSVT), while other types of CNS events were less clearly defined (Caruso et al. 2006). In their review, Athale and Chan (2003a) reported that 52 % of CNS events were CSVT, with 43.7 % parenchymal lesions and 4.3 % combined. The etiology of CNS thrombosis in children with cancer is likely multifactorial and related to direct tumor invasion, chemotherapy-induced hypercoagulability, and associated complications like dehydration and infection (Wiernikowski and Athale 2006). Non-CNS events in the meta-analysis by Caruso et al. (2006) included deep vein thrombosis (DVT, 43 %), pulmonary emboli (PE, 2 %) and right atrial thromboses (2 %). DVT was noted to be more common in upper than lower extremities, most in association with a CVC (Caruso et al. 2006). The majority of thromboses are venous, with only 3 % of events reported as arterial in the review by Athale and Chan (2003a). In 5 % of cases, thromboses were multifocal and 50 % of TE occurred in potentially life-threatening locations (Caruso et al. 2006). Thrombosis accounts for a relatively small fraction of treatment-related mortality, with reports ranging from 0 to 4.8 %, largely from PE and CNS events (Athale and Chan 2003a). Very little evidence exists about morbidity from TE in pediatric ALL; one study of pediatric ALL survivors reported a 50 % prevalence of post-thrombotic syndrome (PTS) following a symptomatic TE (Kuhle et al. 2008). PTS includes symptoms of pain, swelling and skin changes to the affected limb. For patients with CNS TE, reports suggest that up to 15–20 % will have residual neurologic deficits, while the effect on neurocognitive outcome is unknown (Athale and Chan 2003a). Others report that full neurologic recovery is the norm (Payne and Vora 2007). Qureshi et al. (2010) reported no permanent sequelae of TE among 59 children with ALL, including those with CSVT who presented with neurologic deficits.

8.3 ALL Risk Factors

Several studies have identified older age as a significant risk factor for TE among children treated for ALL (Athale and Chan 2003a). An analysis of 91 patients treated at McMaster Children's Hospital following Dana Farber Cancer Institute (DFCI) protocols for ALL found that 7 of 16 patients ≥10 years (44 %) developed symptomatic TE versus 3 of 75 (4 %) in younger patients (Athale et al. 2005). Patients classified with high-risk ALL also appear more likely to develop TE, though this is confounded by the effect of age, as older children are considered high-risk by definition. In the same McMaster study, 26 % of the 35 high-risk patients developed TE (11 % of those <10 years) versus 2 % of 56 standard-risk patients. The effect of gender on the risk of TE has been less clear, with contradictory reports published; in the McMaster study, gender did not influence risk of TE (Athale and Chan 2003a; Athale et al. 2005). The presence of a CVC is a well-established risk factor for TE in the general pediatric population as well as in ALL; half of all symptomatic DVT in children with ALL are associated with a CVC (Athale and Chan 2003a).

Table 8.1 Summary of treatment strategies and level of evidence for the management of thrombosis in pediatric oncology patients[a]

Clinical scenario	Recommendations	Level of evidence[b]
Primary thromboprophylaxis	Not recommended (including LMWH, warfarin, FFP)	1B
	Routine screening with coagulation studies or for thrombophilia not recommended	2C
	Thrombophilia screening can be considered for patients with known TE risk factors	2C
Development of a non-CVC-related thrombosis	Thrombophilia screening	2C
Thromboembolism	Treatment with LMWH	2B
	Thrombolysis with tPA or thrombectomy for life- or limb-threatening thrombosis	2C
	Warfarin generally not recommended but can be considered with long-term anticoagulation	2B
	Treatment for a minimum of 3 months and until the precipitating factor has resolved	2C
	Consideration for holding asparaginase therapy during acute TE	2C
	If nonfunctioning or no longer needed, the CVC should be removed after 3–5 days of anticoagulation	1B
	If functioning and clinically necessary, the CVC can remain with continuing anticoagulation	2C
Cerebral sinovenous thrombosis	Total anticoagulation for at least 3 months	1B
	Continued anticoagulation for 3 additional months if with persistent occlusion or symptoms	2C
	If with hemorrhage, anticoagulation can be reserved for cases with thrombus extension	2C
	Prophylactic anticoagulation should be given with subsequent asparaginase doses	2C
Thrombocytopenia with anticoagulation	Initially transfuse to keep platelets >20–50 × 10^9/L	2C
	Subsequently, hold anticoagulation for platelets <20–50 × 10^9/L	2C
Lumbar puncture with concomitant anticoagulation	LMWH should be held 24 h prior and resumed 12 h after LP	1C

LMWH low-molecular-weight heparin, *FFP* fresh frozen plasma, *TE* thromboembolism, *CVC* central venous catheter, *tPA* tissue plasminogen activator, *LP* lumbar puncture

[a]See text for full detail

[b]Per Guyatt et al. (2006); see Preface

Multiple studies have reported the association of genetic prothrombotic defects and ALL, including factor V Leiden, prothrombin gene G20210A mutation, MTHFR C677T and A1298 mutations, deficiencies of protein C, protein S, or antithrombin (AT), and high lipoprotein (a) levels. In the largest study, Nowak-Göttl et al. (1999) prospectively evaluated inherited thrombophilia traits in 301 children enrolled on ALL Berlin-Frankfurt-Muenster (BFM) 90/95 protocols. Eleven percent of patients with complete follow-up experienced a symptomatic TE, and the presence of an inherited thrombophilia significantly increased the risk: 46.5 % with an identified prothrombotic defect experienced a TE versus 2.2 % without such a defect. The greatest risk was associated with protein C, protein S and AT deficiency (Nowak-Göttl et al. 1999). In contrast, the North American PARKAA study prospectively evaluated the prothrombin 20210A mutation and factor V Leiden in 60 children with ALL and correlated with screening radiography but found no association with TE (occult or symptomatic), though four of eight patients

with antiphospholipid antibodies did experience thrombosis (Mitchell et al. 2003b). Caruso et al. (2006) reviewed five prospective studies reporting prothrombotic genetic defects; the prevalence of mutations was similar to the general population and the pooled relative risk of TE with thrombophilia was 8.5. It remains unclear as to why studies of risk in children with thrombophilia have shown such variable conclusions (Raffini and Thornburg 2009).

Much of the literature regarding thrombosis in ALL patients centers on the use of L-asparaginase. Asparaginase catalyzes the hydrolysis of the amino acid asparagine to aspartic acid and ammonia. The rapid depletion of the circulating pool of asparagine reduces hepatic protein synthesis, which in turn causes a decrease in natural anticoagulants such as AT, fibrinogen, and plasminogen, as well as protein C and S. The coagulopathy associated with asparaginase may result in both thrombosis and hemorrhage, although the former is much more common (Athale and Chan 2003b). The pharmacology of asparaginase is affected by its source (*Escherichia coli* or *Erwinia chrysanthemi*), different commercial manufacturers (European, Japanese, American), and modifications (polyethylene glycosylated; PEG-asparaginase), with profound effects on half-life, asparagine depletion and protein synthesis inhibition. Comparison of published rates of TE associated with asparaginase is hampered by this variability as well as by variations in dosage, timing of administration, and concomitant chemotherapy. In the meta-analysis by Caruso et al. (2006), the rate of TE was significantly decreased with doses of $\geq$10,000 units/m^2 vs. $\leq$6,000 units/m^2 and with <9 days of asparaginase exposure; type of asparaginase or manufacturer did not show significant differences.

PEG-asparaginase, formed by covalently attaching polyethylene glycol to the native *E. coli* asparaginase enzyme, is now more commonly used in ALL therapy protocols and was associated with a 2 % risk of thrombosis in a study of 197 patients treated from 2005 to 2007 following a DFCI protocol including prednisone during induction (Silverman et al. 2010). Qureshi et al. (2010) reported venous thrombosis in 3.2 % of 1,824 patients treated on the British UK ALL 2003 protocol using PEG-asparaginase and dexamethasone during induction and delayed intensification. Ninety percent of events occurred during PEG-asparaginase exposure, 70 % of which were during induction. Although CVC placement was deferred to the end of induction on this protocol to reduce the risk of CVC-associated TE, 50 % of events were CVC related, while 36 % involved the CNS and the remainder were DVTs (Qureshi et al. 2010). All patients recovered completely without clinical sequelae, and 73 % received subsequent asparaginase (the majority with prophylactic LMWH) with no recurrent TE or excess bleeding. Intravenous PEG-asparaginase has been reported to have a similar rate of thrombotic complications as intramuscular administration (Silverman et al. 2010).

The effect of asparaginase may be further augmented by the concurrent use of corticosteroids during ALL induction, which can also increase the VTE risk eight to tenfold (Nowak-Göttl et al. 2009; Mitchell et al. 2010). In a prospective cohort study of 420 ALL patients enrolled on separate German cooperative protocols, symptomatic TE occurred in 11.6 % of those treated with concurrent prednisone and *E. coli* asparaginase in induction versus 2.5 % among those who received asparaginase in consolidation without prednisone (Nowak-Göttl et al. 2001). Steroids increase the level of prothrombin as well as factor VIII, von Willebrand factor, PAI-1 and AT (Harlev et al. 2010). Some evidence exists for a lower risk of TE with prednisone versus dexamethasone; 10.4 % of children receiving dexamethasone during induction on the BFM 2000 protocol developed TE compared with 1.8 % of those who received prednisone on the earlier BFM 90/95 protocols despite similar asparaginase dose and schedule (Nowak-Göttl et al. 2003). Caruso et al. (2006), however, showed no difference in rate of TE between prednisone and dexamethasone in induction although prednisone led to a significant increased risk in postinduction phases. Further data are required to make firm conclusions regarding the effect of steroids on thrombosis risk in pediatric ALL patients.

8.4 Other Malignancies

Data regarding TE in pediatric malignancies other than ALL are limited. Overall, more than 40 % of pediatric oncology patients with TE have a diagnosis other than ALL, and the prevalence among non-ALL cancers is about 16 % (Wiernikowski and Athale 2006). Lymphoma and sarcoma have an increased risk of TE, while brain tumors do not (Athale et al. 2008b). As in children with ALL, children with other malignancies are at significantly increased risk of TE if older and if with CVC dysfunction; mediastinal disease is a significant risk factor in children with lymphoma with a trend toward increased risk in patients with more extensive disease (Athale et al. 2007; Athale et al. 2008a).

A 2008 retrospective study of 75 children diagnosed between 1999 and 2004 with Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) reported 9 patients (12 %) with 16 thrombotic events (Athale et al. 2008a). Twelve of these events were venous and there was a 2.6 % rate of PE (Athale et al. 2008a). Sixty-nine percent were associated with a CVC and none were CNS events, in contrast with the distribution in ALL patients. However, it has been reported separately that 1–3 % of patients with advanced NHL develop CSVT (Wiernikowski and Athale 2006). In multivariate analysis, mediastinal involvement increased the risk of thrombosis; 9 of 51 patients with mediastinal lymphadenopathy developed TE versus none of 21 patients without mediastinal involvement (Athale et al. 2008a). Lymphoma type, gender, presence of B-symptoms, age and stage were not risk factors for TE in lymphoma patients. Notably, despite the use of asparaginase, children with NHL did not appear to be at higher risk for TE than children with HL, contrasting results in adults (Wiernikowski and Athale 2006; Athale et al. 2008a). The meta-analysis additionally noted a 40 % recurrence rate (four patients); of these patients, only two had received secondary thromboprophylaxis with coumadin or LMWH and both had TE recurrence while on coumadin.

A retrospective cohort study investigated thromboses in 122 children and adolescents with soft tissue sarcoma treated at the National Cancer Institute from 1980 to 2002 (Paz-Priel et al. 2007). The authors reported 23 thromboembolic events in 19 patients and an overall TE incidence of 16 %. Over 50 % of the TE were detected at the time of initial cancer evaluation and 57 % were symptomatic. Thirty-five percent of thromboses were related to tumor compression and 13 % CVC associated. Involved sites included extremity DVT (43 %), PE (22 %) and inferior vena cava (17 %). Patients with distant metastasis were 2.5 times more likely to have a clot, 23 % vs. 10 %, with a trend towards significance (Paz-Priel et al. 2007). The rate of TE was similar for all types of sarcoma and between children and young adults. Though thrombophilia was infrequently investigated, four patients had lupus anticoagulant detected. In another single-institution retrospective analysis of pediatric sarcoma patients treated between 1990 and 2005, 10 of 70 patients (14.3 %) developed symptomatic TE (all DVTs), six of which were CVC associated (Athale et al. 2007). CVC dysfunction significantly increased the risk of TE: 55 % of those with CVC problems developed TE versus 8.2 % in those without. Prevalence of TE was increased in patients with pulmonary disease, metastases, older age and Ewing sarcoma, but these factors failed to reach statistical significance. Relapse and death were more common in patients with symptomatic TE but again without reaching statistical significance.

In adults with malignant brain tumors, the risk of TE is 20 % in the perioperative period without prophylaxis and risk remains high throughout treatment, reaching 28 %, particularly in adult patients with malignant gliomas (Wiernikowski and Athale 2006). TE is comparatively much less common in children with CNS tumors (Athale et al. 2008b). Tabori et al. (2004) reviewed 462 pediatric patients with malignant brain tumors over 14 years in Israel and only three (0.6 %) had symptomatic VTE. All were severely debilitated at the time of TE diagnosis, likely stemming from complications of their underlying malignancy (Tabori et al. 2004). In a report of 253 patients treated at St. Jude Children's Research Hospital, the frequency of symptomatic TE was 2.8 %, with increased risk associated with CVC dysfunction (Deitcher et al. 2004). Athale et al. (2008b) reported a significantly lower prevalence of TE in patients with CNS tumors than other groups, with

Table 8.2 Summary of known and presumed risk factors for thromboembolism in pediatric oncology patients[a]

Known risk factors[b]	Type of malignancy
	ALL
	AML
	Lymphoma
	Sarcoma
	Older age
	Presence of central venous cathether
	Dysfunction of central venous catheter
	Asparaginase therapy in ALL
	Steroid therapy in ALL
	Blood vessel compression by bulky solid tumor
Presumed risk factors[c]	Type of malignancy
	Other solid tumors including Wilms tumor and neuroblastoma
	Thrombophilia
	History of thromboembolism
	Concomitant asparaginase and steroids in ALL
	Mediastinal involvement in lymphoma patients
	Solid tumor patients with extensive metastatic disease
	Sepsis
	Surgery
	Immobilization
Not risk factors[d]	CNS tumors
	Gender

ALL acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *CNS* central nervous system
[a]See text for detail
[b]Consistent significant multivariate analysis proving risk
[c]Inconsistent results; trend towards significance
[d]Consistent significant analyses proving not a risk factor

one event among 201 children with CNS tumors. A summary of known and presumed risk factors for TE is presented in Table 8.2.

8.5 Central Venous Catheters

CVCs are essential in pediatric oncology but associated with risk of infection and thrombosis. The actual incidence of TE in children with CVCs for cancer treatment is unknown, with a wide range in reported rates due to variation in definitions, diagnostic methods and populations studied (Wiernikowski and Athale 2006). Most CVC-related thromboses are asymptomatic and located at the entry site of the catheter into the vein (Nowak-Göttl et al. 2009). The morbidity of these asymptomatic catheter-associated thromboses is unknown. Glaser et al. (2001) reported evidence of thrombosis in 12 of 24 asymptomatic pediatric oncology patients with implantable CVCs (ports) screened by contrast venography. As mentioned, the PARKAA study reported a prevalence of 37 % in children with ALL and indwelling CVCs screened radiographically after induction therapy, but only 5 % had clinical symptoms (Mitchell et al. 2003b). Symptoms may include swelling, pain, tenderness, erythema or discoloration of the affected limb, or dilated vessels. CVC-related TE can lead to recurrent TE (4–19 %), PE (8–15 %), PTS (5–25 %), and death (2–4 %) (Nowak-Göttl et al. 2009). The mechanisms by which CVCs may lead to TE include changes to venous flow dynamics, trauma to the vessel wall, or hyperosmolar substances such as parenteral nutrition or chemotherapy (Wiernikowski and Athale 2006). External tunneled CVCs are more likely to develop thrombosis than implanted catheters (ports); a retrospective analysis of 362 patients with ALL enrolled on a Pediatric Oncology Group (POG) protocol noted that external CVCs were 3.9 times more likely to be associated with thrombosis than internal catheters (McLean et al. 2005). In a prospective study, Male et al. (2003) showed significantly increased risk of TE with CVC placement on the left side, in the subclavian vein and when inserted percutaneously. Some institutions and protocols have recommended delaying the insertion of a CVC until the end of induction therapy for ALL to minimize risk, but acceptance of this policy has been variable and it remains unclear if timing of CVC insertion is a risk factor for TE (McLean et al. 2005; Astwood and Vora 2011).

8.6 Diagnosis

The medical complexity of pediatric oncology patients and the often subtle or nonspecific signs and symptoms of TE mandate a high index of suspicion. Although the "gold standard" for diagnosis

of DVT in adults is bilateral venography, in clinical practice it is infrequently used in children due to technical difficulties, the need for iodinated contrast, and the possibility of inducing or extending thrombus (Manco-Johnson 2006). Doppler ultrasound is useful for assessment of lower extremity DVT and for jugular and distal upper extremity veins, but is less sensitive for proximal upper system thrombosis. The PARKAA study documented low sensitivity (20 %) of ultrasound for superior vena cava (SVC) and proximal subclavian thrombosis compared to venography, though the latter was inferior for internal jugular thrombosis (Mitchell et al. 2003b). Magnetic resonance imaging (MRI) with angiography/venography (MRA/MRV) or computed tomography (CT) with intravenous contrast are useful when ultrasound cannot be reliably performed. MRI with MRA/MRV is the modality of choice for evaluating CNS thrombosis. Echocardiogram may be used for evaluation of proximal SVC and cardiac thrombosis. High-resolution spiral CT scan with contrast is most commonly used for diagnosis of PE in children, but ventilation/perfusion (V/Q) scans may be used as well (Wiernikowski and Athale 2006).

8.7 Management

8.7.1 Prevention

Although several professional organizations have published guidelines for VTE prophylaxis in adult oncology patients, evidence-based guidelines for prevention in children with cancer are lacking. The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and others have recommended prophylactic anticoagulation for all hospitalized oncology patients and for high-risk surgical oncology patients, but not for ambulatory cancer patients with or without CVCs (Khorana et al. 2009). These guidelines, developed for adults with a very different range of malignancies, comorbidities, and treatments than seen in children, are clearly not directly applicable to the pediatric oncology population.

Evidence from clinical trials of thromboprophylaxis in children with cancer is limited and generally inconclusive. The Prophylaxis of Thromboembolism in Kids (PROTEKT) trial randomized 186 children with CVCs, half with cancer, to receive reviparin LMWH prophylaxis or standard care. There was no difference in the rate of TE or adverse events, but the study was underpowered and terminated early due to slow accrual (Massicotte et al. 2003). The PARKAA trial randomly assigned 85 patients treated for ALL on contemporary North American protocols to receive weekly infusions of AT during induction with asparaginase. Twenty-eight percent of patients treated with AT developed TE versus 37 % in the control group, but the study was underpowered to show a significant difference, and no difference was seen in markers of endogenous thrombin generation (Mitchell et al. 2003a). Supplementation with fresh frozen plasma (FFP) has been shown to be ineffective in correcting hemostatic parameters in children treated with asparaginase (Nowak-Göttl et al. 2009). Ruud et al. (2006) reported no reduction in the incidence of CVC-related jugular thrombosis among 62 children with cancer in a randomized, placebo-controlled study of low-dose warfarin prophylaxis.

Several small cohort studies and case series have reported various methods of thromboprophylaxis. Harlev et al. (2010) screened 80 children with ALL for inherited thrombophilia and provided enoxaparin prophylaxis during induction for 18 patients with prothrombin gene mutation or factor V Leiden heterozygosity. Six patients (7.5 %) developed TE, half of whom had PT mutation and were receiving prophylaxis. Elhasid et al. (2001) prescribed enoxaparin prophylaxis during asparaginase treatment to 41 consecutive children with ALL and reported no episodes of TE and no bleeding but with no comparative control group. Meister et al. (2008) reported no episodes of TE in 41 children treated on BFM ALL trials with AT supplementation and enoxaparin prophylaxis in induction and reinduction versus 13 % of 71 patients in an earlier cohort treated on the same protocol with AT supplementation alone. Mitchell et al. (2010) recently reported validation of a predictive model for identifying the risk of TE in children with ALL treated on Berlin-Frankfurt-Munster (BFM), Cooperative Acute Lymphoblastic Leukemia (COALL) and French Acute

Lymphoblastic Leukemia (FRALLE) induction protocols. The model incorporates factors including concomitant asparaginase with steroids, presence of a CVC and genetic thrombophilia. Eight high-risk patients received enoxaparin prophylaxis during induction at their physicians' discretion and one developed TE as compared with eight events among 11 high-risk patients who received no thromboprophylaxis (Mitchell et al. 2010). Of note, this predictive model was protocol specific (no high-risk patients on the FRALLE protocol experienced TE) and would require further study before application in the context of current North American or other protocols.

The small size, variability and design of these studies constitute significant limitations. At this time, there is insufficient evidence to recommend routine thromboprophylaxis in children with cancer. The American College of Chest Physicians (ACCP), in its 2012 clinical practice guidelines for antithrombotic therapy in children and neonates, recommends against the use of routine systemic thromboprophylaxis for children with short- or medium-term CVCs (Monagle et al. 2012). Without evidence to support any benefit of prophylactic FFP or AT replacement, routine screening of coagulation tests during ALL induction therapy is not recommended. Similarly, routine screening of children with ALL (or other malignancies) for inherited thrombophilia is not currently advised outside of a clinical trial, but may be appropriate for patients with a confirmed family history of a high-risk genetic defect (Astwood and Vora 2011). Secondary screening may be considered for patients at the time of diagnosis with symptomatic TE. At our institution, patients who develop a non-CVC-associated thrombosis are usually tested for factor V Leiden, prothrombin G20210A mutation, protein C and S deficiency, AT deficiency, lipoprotein (a), fasting serum homocysteine, factor VIII, and antiphospholipid antibodies.

Prophylaxis may be considered for select groups of patients at increased risk, including those with known inherited prothrombotic defects who are receiving asparaginase, adolescents undergoing major surgery or prolonged immobilization, and patients with a previous history of TE with other risk factors such as surgery or disease relapse (Wiernikowski and Athale 2006). Evidence-based data to support these considerations in pediatric patients are lacking.

8.7.2 Treatment

LMWH is the anticoagulant of choice for most pediatric patients, offering advantages of reduced monitoring, minimal drug or diet interactions, and a favorable safety profile (Monagle et al. 2012). The REVIVE (reviparin in childhood venous thromboembolism) trial is the only randomized study of LMWH in pediatrics (Massicotte et al. 2003). This trial compared reviparin to unfractionated heparin (UH) and oral anticoagulation in children with TE but terminated early due to slow enrollment. Though underpowered, it contributed to other accumulating evidence that LMWH is safe and effective treatment for TE in pediatrics (Massicotte et al. 2003). Alternatives include UH, which may be preferred initially over LMWH in circumstances of increased bleeding risk where rapid reversal may be necessary. Systemic or catheter-directed thrombolysis with tissue plasminogen activator (tPA) may be considered in some cases of high-risk thrombosis, though experience in children, particularly in the setting of malignancy, is very limited. The 2012 ACCP guidelines suggest tPA use only for life- or limb-threatening thrombosis in children (Monagle et al. 2012). Warfarin is often problematic in children with cancer because of problems related to dosing, drug interactions, vitamin K variability, and difficulty of oral administration during episodes of nausea and mucositis. It is generally not recommended for children during treatment for cancer, but can be considered for long-term or indefinite anticoagulation, when required.

In their 2012 guidelines, the ACCP suggests that children with cancer who develop TE follow the general recommendations for children with TE, using LMWH for a minimum of 3 months and until the precipitating factor has resolved (Monagle et al. 2012). In the acute setting of symptomatic TE, LMWH such as enoxaparin

should be initiated twice daily at 1–1.5 mg/kg/dose subcutaneously and adjusted to maintain an anti-Xa level of 0.5–1.0 units/mL in a sample taken 4 h after injection (Manco-Johnson 2006). Whether a minimum of 3 months of LMWH treatment is necessary in a TE that resolves quickly is unknown and more rapid transition to prophylactic dosing may be reasonable (Manco-Johnson 2006).

Patients may transition to once-daily prophylactic dosing (although ideal prophylactic dosing remains q12 h), with a target anti-Xa level of 0.1–0.3 units/mL (although anti-Xa levels do not generally need to be followed with prophylactic dosing), upon recanalization or after 3–6 months (Manco-Johnson 2006; Nowak-Göttl et al. 2009). Prophylaxis should continue throughout asparaginase therapy until 48 h after the last dose or 2 weeks after PEG-asparaginase (Payne and Vora 2007). Due to noted worse outcomes in patients receiving less asparaginase, the general recommendation is to temporarily suspend asparaginase after TE diagnosis and restart at a later point with concomitant anticoagulation (Silverman et al. 2001; Grace et al. 2011). In the analysis of Dana Farber Cancer Institute (DFCI) consortium data, Grace et al. (2011) reported that 77 % of patients restarted asparaginase with 17 % of pediatric patients having recurrent TE following this methodology. The ACCP guidelines also recommend continuing prophylactic dosing of anticoagulation until CVC removal, with therapeutic dosing if there is a recurrence of TE until 3 months after CVC removal. Clinicians will need to take into consideration the need for surgery, chemotherapy and other treatments that may modify the risk-benefit ratio for the treatment of TE during this period. If nonfunctioning or no longer needed, the CVC should be removed after at least 3–5 days of anticoagulation, but if functional and still clinically necessary, the CVC can remain in situ with anticoagulation as described above (Monagle et al. 2012).

Optimal dosing of unfractionated heparin (UH) is poorly defined in children and has been extrapolated from adult data. If UH is initially used, the ACCP recommendation is to bolus with 75 units/kg IV over 10 min, then start an initial maintenance dose of 20 units/kg/h for patients >1 year of age (28 units/kg/h for infants). Activated PTT should be monitored 4 h after the loading dose and 4 h after every change in infusion rate. The rate should be adjusted to maintain an aPTT of 60–85 s (2–3 times upper limit of normal; unfractionated anti-Xa level of 0.35–0.7 units/mL). Once therapeutic aPTT levels are obtained, monitoring requires a daily CBC and aPTT. Plasminogen and antithrombin should be monitored and repleted to ensure heparin efficacy; D-dimers can be measured to monitor response and fibrinogen should be followed and repleted to prevent bleeding complications. Boluses should be withheld if there is a significant bleeding risk (Monagle et al. 2012).

In the case of life-threatening TE, the ACCP recommends thrombectomy along with therapeutic anticoagulation. In the setting of lower extremity VTE where anticoagulation is contraindicated, a retrievable IVC filter may be placed temporarily. For children with CVC-associated right atrial thrombosis, catheter removal with or without anticoagulation is recommended, while anticoagulation is encouraged and, potentially, if the thrombus is large (i.e., >2 cm) and mobile, with CVC removal and consideration for surgical intervention or thrombolysis as indicated (Monagle et al. 2012). For children with CSVT without significant intracranial hemorrhage, the ACCP recommends initial anticoagulation with UH or LMWH and total anticoagulation for at least 3 months, continuing for 3 additional months for persistent occlusion or symptoms. If there is significant hemorrhage, anticoagulation may either be initiated or reserved for cases with thrombus extension after 5–7 days. Surgical intervention or thrombolysis is reserved for patients who show no improvement on initial anticoagulation therapy (Monagle et al. 2012).

Necessity of reduction or cessation of anticoagulation during periods of thrombocytopenia is unstudied, and decisions should be tailored to individual circumstances. During initial therapeutic anticoagulation, platelets may be transfused to maintain a platelet count of $>20–50 \times 10^9$/L (Manco-Johnson 2006; Nowak-Göttl et al. 2009).

Safe LMWH dosing in the stable pediatric oncology patient with thrombocytopenia is unclear; our institutional practice is to hold LMWH with platelet counts $<50 \times 10^9$/L although other treatment strategies may be equally valid. Enoxaparin should be held 24 h before lumbar punctures or other procedures and resumed 12 h later or 24 h after neurosurgery (Manco-Johnson 2006; Wiernikowski and Athale 2006).

8.8 Summary

TE is a common and significant complication of childhood cancer, though the exact incidence remains unknown. Most evidence pertains to children with ALL, but those with solid tumors and other hematologic malignancies are also affected. The most important risk factors include older age, presence of a CVC, CVC dysfunction, asparaginase treatment, and intrathoracic or metastatic disease in solid tumors. Clinical features and diagnosis of TE are similar in cancer to the general pediatric population, with a predominance of catheter-associated venous thromboses and, in ALL, sinovenous thrombosis. Screening for inherited thrombophilia or for asymptomatic TE is not recommended, and there is insufficient evidence to support primary prophylaxis with anticoagulation or clotting factor support. Management of symptomatic TE in children with cancer should follow established general pediatric guidelines but presents particular challenges due to the additional risks of bleeding, ongoing therapy and underlying malignancy. LMWH is the treatment of choice for TE in pediatric oncology with anticoagulation continuing while risk factors, such as a CVC or asparaginase therapy, persist. Dose adjustment during periods of thrombocytopenia or with invasive procedures may be required. Despite an abundance of data regarding thrombosis in adults with cancer, there is relatively little evidence to guide the management of TE in children with malignancy. More research is urgently needed to better understand the epidemiology and risk factors for thrombosis in these children and to develop strategies for prevention and optimal therapy.

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