Section 1 Epidemiology, etiology, diagnosis, treatment, outcomes

Chapter 1

Extremity and caval deep venous thrombosis

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Introduction

Advances in supportive care have changed the landscape of clinical pediatrics from acute life-threatening conditions to more chronic diseases. Venous thromboembolism (VTE), comprising of deep venous and thrombosis (DVT) and pulmonary embolism (PE), traditionally considered as an acute and chronic disease of the elderly, is increasingly recognized in hospitalized children and has emerged as a significant public health burden. Although the incidence of pediatric thrombosis is lower than that in adults, over the last few decades it has been recognized that pediatric thrombosis has become a substantial health hazard and may be associated with significant morbidity and mortality. Additionally, the health-care burden of VTE may be particularly high for affected children, given the additional impact imposed on the child's family members and by the much greater life expectancy compared with affected elderly adults. Evidence-based recommendations for management of pediatric thrombosis are still lacking, due to lack of large carefully conducted clinical trials and most recommendations are either directly extrapolated from adults or are based on consensus or expert opinions [1]. As the incidence of pediatric thrombosis increases and newer anticoagulant drugs make their way into the clinical field, investigators have felt the necessity for improved diagnostic testing, risk adapted treatment regimens and better definitions of outcome measures after pediatric thrombosis [2]. This chapter focuses on recent knowledge and current advances in pediatric extremity and caval thrombosis.

Epidemiology

Over the last two decades, pediatric VTE has become required as an increasingly frequent complication. The estimated incidence from the Canadian Childhood Thrombophilia registry as originally reported in 1994 was 0.07/10,000 children per year as compared to 5.6–16 cases/10,000 adults per year [3]. However, it is now estimated that pediatric VTE is approximately ten-fold more common than the initial estimates from the Canadian registries. The population prevalence of pediatric VTE in the USA is estimated to be 0.6–1.1 per 10,000 and recent epidemiologic analysis of both the Kid's Inpatient Database (KID) and the Pediatric Health Information System (PHIS) have estimated the incidence to be as high as 42–58/10,000 hospital admissions [4–6]. The analysis of the KID has also demonstrated that the majority of childhood VTE events occur in a tertiary care inpatient setting as compared to community hospitals caring for children (40.2/10,000 vs. 7.8/10,000 admissions). This increasing trend is attributable to the increasing use of central venous catheters (CVCs) for supportive care of children, better imaging techniques for thrombus detection, increasing awareness of the problem and thus lower threshold for screening survival, and improvement in incidence of critically sick children.

Pediatric VTE shows a bimodal age pattern. The highest incidence of pediatric VTE is seen in neonates and infants with a second peak seen in adolescents, particularly teenage girls either in relation to pregnancy or the use of hormonals [7]. Another study demonstrated that the highest VTE risk for non-hospitalized children was in children > 11 years of age as compared to the hospitalized children, where the highest incidence is seen ages < 1 years and > 11 years [8].

Upper and lower extremity and superior and inferior vena caval (SVC, IVC) DVT are the most common sites for thrombosis in children. According to the analysis of the PHIS database, of the specific sites identified, the proportion of VTE cases represented by upper extremity DVT was 15.7%, lower extremity DVT 21% and vena caval thrombosis 18.3% [6].

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From an analysis of the Health Cost and Utilization Project using KID in 2006, the occurrence of lower extremity DVT was estimated to be 29.5% [9].

Etiology and risk factors

Pediatric VTE is a multifactorial disease with a higher incidence in children with chronic or complex medical conditions. The etiopathogenesis of VTE is best explained by the Virchow's triad. In 1845, Virchow postulated that three factors were important in the development of thrombosis: (1) impairment of normal laminar blood flow, (2) endothelial or vascular injury and (3) alterations of the blood (hypercoagulability). Common risk factors for pediatric VTE are listed in Table 1.1. Many of the conditions listed in Table 1.1 may cause thrombosis by affecting more than one factor of the Virchow's triad mentioned above. Venous thromboembolism can be classified as provoked or non-provoked (also called spontaneous) depending on the presence of a proximate identifiable triggering risk factor such as surgery, presence of a CVC, initiation of hormonal contraception, etc. Such events may occur with or without an underlying prothrombotic condition (e.g., genetic or acquired thrombophilia, chronic inflammatory disease) and may have an additive effect on the risk of thrombosis imparted by an underlying prothrombotic condition. However, all children with a proximate triggering event may have an underlying prothrombotic condition and thus it is important to note the subtle difference in terminology. A VTE may be provoked but not have an underlying prothrombotic condition. On the other hand, a child with underlying prothrombotic condition (e.g., a potent inherited thrombophilia trait, such as homozygous factor V Leiden) may present without a proximate triggering factor (unprovoked DVT). True idiopathic DVT, which implies an absence of either a provoking risk factor or an underlying prothrombotic condition, can also exist but is rare in children. In children, the majority of VTE is associated with an underlying associated disorder (76.2% according to a recent analysis of the KID database) [9]. This is in contrast to VTE in adults, where up to 40% of episodes may be idiopathic. Other studies have reported the proportion of VTE represented by idiopathic cases to be approximately 5% in children and < 1% in neonates [7]. The presence of a CVC is the most common provoking risk factor for the development of DVT in children. It is estimated that approximately 60% of the cases of DVT in children and > 90% of cases in neonates are associated with CVC. According to an analysis of the KID database, the most common complex medical conditions associated with VTE were cardiovascular conditions (18.4%), malignancies (15.7%) and neuromuscular conditions (9.9%) [9]. These rates are similar to those reported by other epidemiologic studies [6,10]. The reader is referred to other chapters for a detailed discussion of pediatric evidence of VTE clinical risk factors and the risk for VTE associated with inherited and acquired laboratory thrombophilias.

Table 1.1 Risk factors for pediatric venous thrombosis (Virchow's triad)

1. **Endothelial damage**
   a. Central venous catheters, ventricular atrial shunts, etc.
   b. Sepsis
   c. Antiphospholipid antibodies
   d. Trauma
   e. Inflammatory conditions (e.g., systemic lupus erythematous, inflammatory bowel disease)
2. **Disruption of the laminar blood flow or stasis**
   a. Post-operative state
   b. Immobility
   c. Anatomical variants (e.g., May–Thurner anomaly, Paget–Schroetter syndrome)
   d. Complex congenital heart disease or cardiomyopathy
   e. Total parenteral nutrition (TPN)
3. **Hypercoagulable state**
   a. Inherited
      Deficiency of protein C, S, antithrombin III
      Factor V Leiden, prothrombin gene mutation
      Elevated homocysteine
   b. Acquired
      Antiphospholid antibodies
      Pregnancy or hormonal supplementation
      Nephrotic syndrome
      Medications (e.g., asparaginase chemotherapy)
      Infections (e.g., varicella)
      Malignancy

Central venous catheters

Since the limitations of peripheral intravenous catheters have become apparent, the frequency of insertion of CVCs has increased. These catheters can be placed in the umbilical vein (UVC) in the neonates or in large central vessels (Hickman or Portacath®, and peripherally inserted central catheter, PICC). As mentioned above, the presence of a CVC is the most common triggering risk for the development of DVT in children. This also explains the difference in the most common site of DVT in adults compared with children. In adults, lower extremity DVT is more common. In children,

upper extremity or more proximal (including superior vena caval) DVT is more common because most CVCs in children are inserted into the upper venous system.

CVCs are critical for supportive care of sick children and have contributed to the significant improvement in outcomes of such children. However, the insertion of a CVC can cause thrombosis by directly disrupting the vascular endothelium, by altering the blood flow and by alteration of the local milieu due to infusion of hypertonic solutions such as total parenteral nutrition (TPN) infusions. The risk of thrombosis with a CVC varies depending not only on catheter and individual patient-related risk factors but also on the reasons/underlying conditions for which the CVC is inserted.

Catheter-related risk factors may be related to the caliber of the CVC in relation to the vessel size, catheter composition, infusate, site, and frequency of access and duration of use. Although there are no well-designed clinical trials that compare the thrombotic risk of differing catheter materials, one study revealed increased risk with polyethylene catheters (70%) as compared to silicone catheters (20%) and polyurethane catheters (17%) [11]. Other studies have confirmed that polyethylene catheters are the most thrombogenic, but found no significant differences between silicone, polyurethane and polyvinylchloride catheters [12–14]. The use of heparin-bonded catheters has been demonstrated to prolong catheter patency (i.e., function), but has not been shown to reduce the risk of thrombosis [15]. In one study that evaluated the risk of VTE in infants with CVC, it was found that catheters in the femoral vein and multiple-lumen catheters were associated with a higher risk [16]. In another multicenter prospective study that evaluated the risk of catheter-associated symptomatic VTE, femoral and subclavian vein CVC were shown to have the highest risk [17]. This study also demonstrated that the incidence of VTE was independent of CVC type (PICC, untunneled CVC, tunneled exteriorized CVC and subcutaneous ports) and CVC size [17]. Some studies have indicated that the risk of thrombosis is also related to the duration of catheter dwell *in situ*. The use of UVC or PICC for > 6 days was associated with a higher risk of thrombosis. In one study, duration of non-tunneled femoral CVC > 14 days was associated with a higher risk of DVT, while another study did not demonstrate this [17,18].

Among children with CVC, neonates are at heightened risk for DVT. Some evidence suggests that, within this subgroup, VTE risk factors include small for gestational age with < 1250 g birth weight, hematocrit > 55% and maternal history of pre-eclampsia [19]. More generally among all children, sepsis and infection appear to be risk factors for CVC-associated DVT [19]. The incidence is highly variable depending on the diagnostic modality and approach (e.g., universal screening identifies more cases than diagnostic evaluation of symptomatic patients). In addition to the physical risk factors for thrombosis, infusion of hypertonic solutions, presence of calcium and high levels of dextrose are additional risk factors. In children on long-term TPN, CVC-related DVT is a significant issue. Retrospective studies have shown the incidence to be 0.2–0.4 per 1,000 catheter days or 20–75% [20]. It is also thought that patients with short bowel syndrome may have a higher incidence of thrombosis as compared to other children on TPN due to high frequency of intraluminal bacterial overgrowth due to dysmotility, which may predispose to a higher risk of catheter infection – a risk factor for development of thrombi [21,22].

Cardiac diseases

Complex congenital heart conditions with or without associated extracorporeal membrane oxygenation (ECMO) are independent risk factors for the development of thrombosis in children. In one prospective observational study, the cumulative incidence of VTE was found to be 3.8% of all children with cardiac disorders admitted to the pediatric intensive care unit (PICU) [23]. In this study, the most common risk factor for thrombosis was the presence of a CVC (in 41% of patients). Other risk factors associated with an increased VTE incidence were unscheduled PICU admissions, age < 6 months, use of ECMO, increased CVC duration with complicated hospital course and single ventricle cardiac lesions. Interestingly, 32% of imaging studies that detected VTE were ordered for symptoms other than those directly attributable to VTE. The role of inherited thrombophilia in children with cardiac conditions and thrombosis has also been investigated. One study found heterozygous factor V Leiden (FVL) mutation in 17.3%, methylenetetrahydrofolate reductase (MTHFR) 677C-T mutation in 28.8% and prothrombin G20210A mutation (PT) in 5.8% of patients [24], while another study found that the overall frequency of FVL and/or PT was 22% in children with cardiac disease and thrombosis [25].

Cancer

In adults, the presence of a malignant disorder greatly increases the risk of thrombosis. In children with cancer, extremity and vena caval thrombosis are the most common sites of DVT due to the presence of a CVC [26], but cerebral sinovenous thrombosis may also be seen, especially in patients with acute lymphoblastic leukemia treated with asparaginase chemotherapy. According to the analysis of the PHIS database, coexistent malignant disorders were seen in 11% of children with VTE [6]. In another study, VTE occurred in 5.3% of adolescents and young adults with cancer [27]. This study also showed that patients with leukemia and sarcomas were at a higher risk of VTE than other malignant disorders. A single-center retrospective study in children revealed the cumulative incidence was as high as 2.1%, with highest occurrence seen in hematological malignancies such as acute leukemia and in teenagers [26]. In a multicenter prospective study in children with cancer, the risk of CVC-related DVT was 4.6% [28]. The pathogenesis of thrombosis in malignant disorders is multifactorial. The risk may be related to the presence of a CVC, type of cancer, chemotherapy medications such as L-asparaginase and dexamethasone and other complications such as sepsis. The reader is referred to other chapters for detailed discussion on cancer-related thrombosis.

Anatomical causes

Although there is a rapidly growing literature on risk factors such as CVCs and cancer in the pathogenesis of pediatric VTE, there is a paucity of data on VTE due to anatomical causes. The development of the venous circulation is complex and many anatomic variants are possible and are found in approximately 1% of adults [29]. Interrupted or absent IVC have also been described in association with DVT [29]. For example, absent IVC was found in 0.3% of healthy individuals and up to 2% of patients with other cardiovascular anomalies [29]. A high index for suspicion should be maintained for anatomical abnormalities or local compression when children present with DVT without a specific provoking factor.

Iliac vein compression syndrome was originally described by May and Thurner in 1957 by using autopsy studies. The May–Thurner syndrome is caused by the compression of the left common iliac vein between the overlying right common iliac artery and an underlying vertebral body. Chronic compression along with the pulsations of the overlying artery may lead to vascular intimal damage and formation of venous "spurs" resulting in acute or chronic venous thrombosis [30]. It is important to identify this anatomical anomaly, which has been described in up to 22–32% of 430 autopsies, as treatment with anticoagulation may not be adequate. Without thrombectomy and endovascular treatment, such as stent placement, individuals with the May–Thurner anomaly may be at increased risk for recurrent thrombosis. Similar "May–Thurner-like physiology" may be seen when the compression occurs due to local lesions such as tumors, lymphadenopathy or ectopic kidney.

Paget–Schroetter syndrome or effort-induced thrombosis of the upper extremity may be seen with involvement of the axillary and subclavian veins as a consequence of strenuous activity involving the arms and chest, as a complication of thoracic outlet syndrome or with a presentation of spontaneous thrombosis in the absence of identifiable thrombosis risk factors. Thoracic outlet syndrome refers to the compression of the neurovascular bundle (brachial plexus, subclavian artery and vein) as it exits the thoracic outlet. The cause of Paget–Schroetter syndrome is usually secondary to an underlying anatomic abnormality at the thoracic outlet such as a cervical rib, musculofascial band or first rib anomalies, but can also simply result from a congenitally narrow course of the subclavian vein between the first rib, clavicle and subclavius muscle – often exacerbated by subclavius muscle hypertrophy in the setting of effort-induced thrombosis. Repeated compression of the subclavian vein leading to venous stasis combined with perivascular fibrosis and endothelial damage due to venous stretching leads to DVT. Anticoagulation alone with or without thrombolysis may lead to high rate of recurrence. Endovascular treatment along with removal of local compression such as cervical rib resection may be necessary to prevent recurrent events [31].

Presentation

Children may present with local pain, swelling or redness of the involved extremity. CVC-related thrombosis is associated with CVC-associated blood stream infection, and therefore a level of suspicion for thrombosis should be maintained in children with CVC-associated blood stream infections, particularly when the latter are refractory/recurrent despite appropriate antibiotic therapy. When thrombosis is associated with a CVC, CVC dysfunction may be an early sign. It is recommended to investigate for DVT in a case of

occluded CVC if the catheter fails to function after two local instillations of a thrombolytic agent [1,32]. Frequently, CVC-related DVT is asymptomatic in children, and may be detected during routine screening or imaging for other procedures. By contrast, patients with CVC-associated thrombosis (sometimes with only a remote history of CVC placement) can develop SVC thrombosis that, when sufficiently occlusive, may present with SVC syndrome characterized by facial and neck swelling and dilatation of superficial collateral venous circulation of the arms, neck and chest, all due to impaired deep venous return in the upper venous system. Children with effort-induced thrombosis of the upper extremity may present after significant use of that arm, e.g., in baseball or basketball practice [31]. Neonates with acute VTE may present with new-onset thrombocytopenia. It is important to note that in patients with a previous history of thrombosis, ruling out a recurrent thrombotic event is warranted if progressive or new symptoms develop. An unequivocal change in the extent of thrombosis, compared with the previous ultrasound scan, might be indicative of new ipsilateral DVT [33].

Diagnosis

Radiologic studies

Compression ultrasound (CUS) with Doppler remains the most common technique for diagnosis of extremity DVT, particularly at and above the level of the popliteal vein in the leg. Advantages of CUS are that it is inexpensive, portable, readily available, requires no sedation and conveys no radiation exposure. The deep veins can be evaluated in transverse and longitudinal scans. The compressibility of the vein can be assessed and failure of the vein to collapse is indicative of the presence of a thrombus. Bulging of the vein also suggests that a thrombus is present. Additionally, color flow and Doppler images should be obtained. Flow deficits can be detected on color flow Doppler [34]. Lack of tissue density on imaging ultrasound with concomitant lack of Doppler flow suggests a fresh or non-echogenic clot. However, several factors such as small diameter of blood vessels, lower pulse pressure in children and the presence of a CVC may interfere with the diagnosis of thrombosis by ultrasound. If clinical suspicion for thrombosis is high, then other diagnostic modalities such as conventional venography, magnetic resonance venography (MRV) or computerized tomography venography (CTV), may be performed after discussion with the radiologist. The CUS technique has also been used for the diagnosis of DVT of the upper extremity and jugular, axillary and distal subclavian veins. However, ultrasound has poor sensitivity for DVT in the proximal subclavian, innominate or SVC. Diagnostic sensitivity of CUS is greatly dependent upon amenability of the vein to compression maneuver, and veins underlying bony structures (e.g., chest wall) are not amenable to compression. 2D echo cardiography can image the heart chambers and often the proximal SVC, and can be used in conjunction with CUS of the distal subclavian and upper extremity veins for a full evaluation of the upper venous system. Alternatively, MRV or CTV may be used for DVT diagnosis in the chest and other central veins, although MRV is more subject to motion artifacts of respiration as well as flow artifacts. Contrast venography (Figure 1.1) is the historical gold standard for the diagnosis of extremity and caval DVT in adults but is infrequently used outside of settings of suspected May–Thurner anomaly, Pagett–Schroetter syndrome or periprocedurally for thrombolytic interventions, due to the invasive technique, requirement for contrast and radiation exposure. Interestingly, the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) study showed that CUS was relatively insensitive in the diagnosis of SVC and proximal subclavian DVT, while venography was insensitive to the diagnosis of internal jugular DVT [35]. Thus it is necessary to tailor the diagnostic

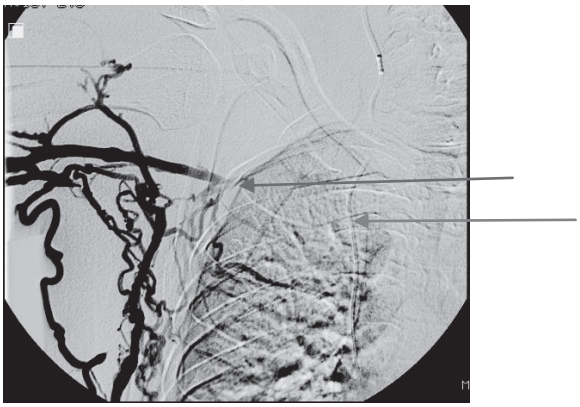

Figure 1.1 Venogram of right upper extremity complete obstruction of the distal subclavian vein (upper arrow) and superior vena cava with extensive collaterals. A central venous catheter (CVC) can also be seen (lower arrow).

modality to the suspected site of thrombosis to accurately diagnose DVT. The MRV and CTV techniques are being used often in many pediatric tertiary care centers for diagnosis of caval, abdominal/pelvic and proximal upper venous system DVT.

Particular attention should be paid to spontaneous DVT. As mentioned above, spontaneous DVT in children is rare. In upper extremity DVT, an anatomical variant such as a cervical rib or a functional thoracic inlet syndrome should be considered in the absence of an obvious predisposing factor. In case of left iliac vein DVT, the diagnosis of May–Thurner syndrome or other anatomical abnormalities should be entertained and appropriate studies should be obtained [29]. Venography is the gold standard for diagnosis of such anatomical variants but, due to limitations mentioned above, may not be feasible in all patients. Positioning of the upper extremity (abduction of at least 30°) is important in demonstration of Paget–Schroetter syndrome [36]. The CTV or MRV methods may be used for diagnosis and should be performed after consultation with the radiologist.

D-dimer

In adults, an elevated D-dimer has been used as a screening test for prediction of VTE. In a patient who has a low clinical index of suspicion for VTE based on history, signs and symptoms, a negative D-dimer can reliably exclude VTE, particularly in the setting of "rule-out" PE. Conversely, in a patient with a high index of suspicion for VTE (particularly PE), a positive D-dimer should prompt diagnostic imaging. However systematic data in children are scarce. One retrospective study in patients < 21 years of age found that the D-dimer test was sensitive (92%) but only moderately specific (57%) for diagnosis of VTE [37]. However, interpretation of D-dimer values need to be made with caution as there are significant age-related differences in the normal range of D-dimer levels [38]. Larger studies are needed to evaluate the role of D-dimer in the diagnosis of pediatric VTE. Given the low incidence of VTE in children in general, D-dimer is likely to play a stronger prognostic than diagnostic role, wherein the latter remains guided by clinical index of suspicion.

Management

Most of the recommendations cited in this chapter are based on extrapolation from adult evidence and on expert opinion [1,32,34]. Children with DVT are in most cases treated with anticoagulation. The aims of anticoagulation in children, based on evidence from adult literature, are to reduce the risk of thrombosis extension or embolization, reduce the incidence of recurrent thrombosis and maintain vessel patency, where clinically relevant. In rare cases, thrombolysis/thrombectomy may be used in an effort to preserve life, limb or organ function, or reduce the incidence/severity of post-thrombotic syndrome (PTS). High-quality evidence is lacking for this last indication, and a large randomized controlled clinical trial of catheter-directed thrombolysis in adult iliofemoral DVT (the ATTRACT trial, NCT 00790335) is ongoing.

Where possible, it is recommended that pediatric hematologists with experience in the field of thrombosis and hemostasis should manage children with DVT [1]. When this is not possible, a combination of a pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist is suggested. This recommendation is based on the known differences in the use of anticoagulant drugs in children compared to adult and on the limited evidenced-based data on the management of thrombotic events in children [1].

Anticoagulation

Currently, the routine anticoagulant agents used in children are unfractionated heparin (UFH), low molecular weight heparin (LMWH) and vitamin K antagonists (VKA). The mechanism of action, pharmacokinetics, therapeutic ranges and monitoring of these anticoagulation methods have been reviewed [1]. The main advantages of UFH are its short half-life and reversal with protamine, both enabling rapid normalization of coagulation in case of bleeding and/or prior to urgent invasive procedures. Thus, in children with DVT who are at higher risk of bleeding or in possible need of an invasive procedure, UFH would be the drug of choice [32].

Initial treatment with UFH or LMWH is recommended for at least 6 days for children with a first DVT [1,32]. For ongoing therapy, the use of either LMWH or VKA (target NR of 2–3) is recommended. For children in whom clinicians will subsequently prescribe VKAs, it is recommended to begin oral therapy as early as day 1 and discontinue UFH/LMWH on day 7 or later than day 7 if the INR is < 2.0 [1].

The LMWHs have become the anticoagulant of choice in children beyond the acute period of DVT (e.g., for outpatient therapy), as well as the

anticoagulant of choice for non-critically ill children presenting with acute thrombosis and normal renal function. The potential advantages of LMWH are reduced need for therapeutic monitoring, lack of interference by other drugs or diet, reduced risk of heparin-induced thrombocytopenia relative to UFH and hypothesized reduced risk of osteoporosis relative to UFH.

The subcutaneous doses required to achieve therapeutic peak anti-factor Xa levels of 0.5–1 IU/ml for enoxaparin, reviparin, dalteparin, tinzaparin and nadroparin in children have been reviewed [1]. In most studies of children with DVT, the LMWH used was enoxaparin. The dose of enoxaparin for children > 2 months of age is 1 to 1.25 mg/kg/dose twice daily and adjusted to achieve the recommended therapeutic levels. In order to decrease the inconvenience associated with twice daily dosing, a once daily enoxaparin regimen of 1.5 mg/kg is sometimes used in adults. A study that evaluated whether a once-daily dosing enoxaparin regimen would be feasible in children showed that in almost half of children the median 24-hour level was below the lower limit of the desired trough range of 0.1 IU/ml anti-Xa activity [39]. In an open-label pilot safety study, 80 children with DVT were treated with enoxaparin with a 4 h post-dose target anti-Xa activity of 0.5–0.8 IU/mL. Following the acute treatment period (7–14 days) children were stratified to receive once daily or twice daily doses. No significant differences were found between the two groups in the occurrence of PTS, VTE recurrence, bleeding and therapy-related death [40].

The safety and efficacy of LMWH in children was summarized in a systematic review and meta-analysis of single-arm studies [41]. The rates of new thrombotic events on LWMH during the acute phase of treatment and the rates of recurrent VTE events on secondary prophylaxis therapy were 2.5% and 3.9%, respectively. The rates of clinically relevant bleeding and minor bleeding were 2.9% and 11.4%, respectively. Safety and efficacy were not associated with age or publication year. The only published multicenter randomized study of anticoagulation for VTE in children used reviparin [42]. The REVIVE (Reviparin in Venous Thromboembolism) trial randomized children with a first VTE to receive either UFH followed by VKAs (target international normalized ratio [INR], 2.5) for 3 months or reviparin (target anti-Xa range, 0.5 to 1.0 units/ml) for 3 months. The study was closed early because of slow accrual. As a result, comparative efficacy and safety between the two regimens remains unclear.

Point of care monitors and educational programs can contribute to the efficacy and safety of, as well as adherence to, VKA therapy in children [43,44]. While no study in children has definitively compared the efficacy and safety of LMWH vs. VKA, meta-analysis data in adults show a statistically non-significant reduction in the risk of major bleeding (OR 0.45; 95% CI: 0.18–1.11) in favor of LMWH [45]. In children, LMWH is often administered through an indwelling catheter (Insuflon™); however, this therapy may be associated with development of hematomas at the site of multiple injections, and theoretically could affect consistency of drug absorption. In spite of this, and due to the relatively difficult management of VKA in children (frequent monitoring, food and drug interaction, etc.), many pediatric hematologists suggest the use of LMWH over VKA, especially for short-term therapy (< 6 months). Longer use of LMWH may be associated with osteoporosis [46], a potential concern that is raised from the much more robust data on the high rate of bone demineralization with pathologic fractures that is associated with the no-longer-recommended long-term use of unfractionated heparin [1]. The VKA may also have a deleterious effect on bone mineralization although data are conflicting.

The decision to use LMWH versus VKA as subacute anticoagulation should be made collaboratively with the patient and family, after weighing pros and cons, in order to achieve optimal adherence and outcome. Use of LMWH may be preferable in infants under 1 year of age [32]. For children with cancer who experience a DVT, LMWH is the preferred anticoagulant because of the relative ease of administering anticoagulation around the usual frequent procedures [1], and due to adult trial findings on LMWH for this indication (e.g., the CLOT and ONCENOX trials) [47–49].

The duration of anticoagulation in children with DVT depends on the clinical circumstance, and is not based upon high-quality pediatric evidence – rather, it is largely extrapolated from adult trials. Clinical experience has indicated that not all pediatric DVT have the same potential for progression or recurrence and that therapy may be based upon risk factors for good or poor thrombotic outcome [34]. For children with unprovoked DVT it is recommended to continue anticoagulation for at least 6 to 12 months. The decision to continue therapy beyond 6 to 12 months may

be based on family and physician preference to avoid the unknown risk of recurrence. The inconvenience of therapy, potential impact of therapy on growth and development and bleeding risk associated with anticoagulation should be taken into consideration in the discussion of anticoagulation duration. In children with recurrent unprovoked DVT, indefinite treatment with VKA is recommended.

For children with provoked DVT (sometimes also called "secondary," but not to be confused with "recurrent" [i.e., second or more] episodes of DVT) in whom the risk factors have resolved, it is recommended to administer anticoagulation therapy for 3 months. If the potentially reversible risk factor has not resolved or been controlled (e.g., ongoing use of CVC, asparaginase therapy, active nephrotic syndrome, etc.), anticoagulation is often continued in either therapeutic or prophylactic doses until the risk factor has resolved. Patients with underlying prothombotic conditions characterized by intermittent symptomatic acute flares of the disease in whom DVT develops during such a flare are often managed, after an initial 3-month course, with episodic secondary prophylaxis during subsequent episodes of symptomatic flare. (Systemic lupus erythematosus is somtimes an exception to the aforementioned paradigm of episodic secondary prophylaxis, wherein an unusually high risk of recurrent VTE may be perceived in this disorder.) Episodic DVT prophylaxis requires that patients are reliable and capable to promptly contact their provider and/or seek medical attention during flares. In patients who experienced asparaginase-associated TE complications, the administration of anticoagulation as secondary prophylaxis for a transient period following subsequent asparaginase doses has enabled this important anti-neoplastic agent to be safely and effectively continued [50,51]. In children with recurrent DVT with an existing reversible risk, anticoagulation is recommended until resolution of the precipitating factor, but for a minimum of 3 months.

In children with CVC-related DVT, management is dependent upon the requirement to maintain the CVC. If the CVC is no longer required, or is not functioning, the CVC should be removed after 3–5 days of therapeutic anticoagulation [1]. If the CVC is required and the CVC is still functioning, it is suggested to keep the CVC and give anticoagulation for 3 months at therapeutic doses. After the initial 3 months, prophylactic doses of VKAs or LMWH are typically maintained until the CVC is removed (Table 1.1). If recurrent DVT occurs while the patient is receiving prophylactic therapy, it is suggested to increase to therapeutic dosing and maintain this regimen for a minimum of 3 months following recurrence and until the CVC is removed [1].

There is no direct evidence to guide the optimal antithrombotic management, including intensity and duration of therapy, for DVT in children with laboratory evidence of thrombophilia. Thus, universal thrombophilia testing after a first episode of DVT in children is not cost-effective when used solely to determine anticoagulation duration [52]. However, some inherited thrombophilias have been associated with increased VTE recurrence risk, and the extrapolated indication of anticoagulation in children is the prevention of recurrent VTE; therefore, evaluation for thrombophilia is not unreasonable in order to inform therapeutic discussions and decision-making with patients/parents, in the absence of RCT-derived evidence on optimal duration of anticoagulation. Nevertheless, according to current guidelines the treatment of DVT in children should not be influenced by the presence or absence of laboratory thrombophilia [1]. An exception to this recommendation may be considered for select case scenarios, such as children with unprovoked DVT who are diagnosed with persistent (positive twice, at least 12 weeks apart) antiphospholipid antibodies (APLA), who should remain on long-term anticoagulation [32,53]. Optimal duration of anticoagulation in children with provoked VTE who meet criteria for antiphospholipid antibody syndrome is less clearly defined. For further detail on considerations for diagnostic evaluation of inherited and acquired thrombophilia in children, the reader is referred to other chapters.

Progression of DVT on therapeutic anticoagulation is a relatively uncommon, but clinically challenging, concern in children. If progression occurs on VKA therapy despite a therapeutic target INR range of 2 to 3, it is recommended to resume UFH or LMWH. Subsequently, therapeutic options include treatment with LMWH at usual therapeutic doses, or switching to VKA using a higher therapeutic INR of 3 to 4 or addition of aspirin to VKA therapy [1]. If progression occurs on LMWH, increasing the dose of LMWH to a higher targeted anti-factor Xa activity can be considered. Severe thrombophilia, such as a high titer APLA or severe deficiency of protein C, protein S or antithrombin, should be considered in children who develop progressive or recurrent thrombosis

while on therapeutic anticoagulation. For further details on the diagnosis and management of children with severe thrombophilia, the reader is referred to other chapters.

Ancillary treatments: thrombolysis and IVC filters

Thrombolytic therapy offers the possibility of achieving more rapid resolution of vessel occlusion than is achieved with conventional anticoagulant therapy but is associated with an increased risk of bleeding. Thrombolysis can be given systemically, catheter-directed or in combination with mechanical thrombectomy. The role of thrombolysis for treating occlusive proximal limb DVT in children is controversial [54]. The UK guidelines recommend considering the use of thrombolytic therapy in children with extensive DVT, particularly those involving the pelvic veins, SVC, IVC and intracardiac sites [32]. Others have suggested systemic thrombolytic therapy for occlusive SVC, IVC and iliac DVT if symptoms are present for no more than 14 days and catheter-directed thrombectomy/thrombolysis if symptoms are present for more than 14 days or there is no recanalization after 24–48 hours of systemic thrombolytic therapy [34]. As the potential bleeding risk associated with thrombolytic therapy is not negligible, when thrombolytic therapy is being considered, management decisions should be made with a multidisciplinary team including pediatric hematologists, interventional radiologists with pediatric experience, pediatric pharmacists and pediatric intensivists [55]. Percutaneous or surgical intervention may be needed for management of DVT secondary to vascular structural abnormalities such as thoracic outlet syndrome, interrupted duplex vena cava, etc. [56]. For children with recurrent DVT secondary to structural venous abnormalities, it is recommended to treat with indefinite anticoagulation unless successful percutaneous or surgical intervention can be performed [1]. For a detailed discussion of thrombolytic modalities and evidence, the reader is referred to other chapters.

The most important indication for the use of IVC filter in both adults and children is the prevention of pulmonary embolism (PE) in patients with lower limb, pelvic, or IVC DVT in whom systemic anticoagulation is contraindicated either on a temporary or long-term basis [32]. Progression of lower limb DVT on adequate anticoagulation therapy may also be an indication for an IVC filter [1]. Prophylactic IVC filter placement may be considered before endovascular thrombolysis for lower extremity DVT. Retrievable filters should be used in children for appropriate indications [57]. Size is a significant limitation and thus an IVC filter would not be suitable for children < 10 kg. The filter should be removed as soon as possible if thrombosis is not present in the basket of the filter and when contraindication to anticoagulation is resolved [1]. A summary of retrospective reports of 61 children (age 7–12 years), who underwent IVC filter placement, found that all reported IVC filter placements were technically successful without any complications [57–59]. Filter retrieval was successful in 22 of 28 attempted (79%) at 1–115 days post-insertion [57,58]. Complications during retrieval included IVC stenosis, successfully treated with angioplasty and contained IVC perforation. Successful insertion and retrieval of IVC filter was reported in three young children (2–3 years of age) [60].

Outcomes

Death

The mortality rate of children with DVT is largely attributed to their underlying disease. In the Canadian Childhood Thrombophilia Registry, the all-cause mortality was 16%, while the mortality rate directly attributable to the DVT event was 2.2% [61]. Similarly, in the Netherlands Registry, the mortality rate directly attributable to DVT was 2% [62].

Thrombus resolution

Vascular recanalization after DVT is believed to possibly help prevent recurrent thrombosis and the development of PTS [63]. Nevertheless, the extent to which thrombus resolution or decrease in thrombus extent is relevant to clinical outcomes remains unclear, both in children and adults. Hence, historically these measures have not been included among the main efficacy outcomes in registration trials of new anticoagulants seeking an indication for VTE treatment.

A series of 160 children consecutively treated for a non-cerebral VTE using enoxaparin for at least 5 consecutive days showed a complete thrombus resolution rate of 48% [64]. The rate of resolution was lower for occlusive compared to non-occlusive thrombus. Age at time of event (neonates vs. non-neonates), location, initial treatment (UFH vs. LMWH) and dose of enoxaparin were not related to outcome [64]. In children

who developed thrombosis during cardiac surgery, the rate of resolution at last follow-up (at least 2 years after surgery) was 62% [65]. Factors associated with thrombus resolution were location (intrathoracic, 75%; extrathoracic arterial, 89%; extrathoracic venous, 60%), non-occlusive thrombi, older age at surgery, higher white blood cell count and lower fibrinogen after surgery. In a series of children with cancer and DVT, the rate of complete thrombus resolution was 67% [49]. Achievement of therapeutic anti-Xa activity was not related to outcome.

Bleeding

Bleeding as a complication of antithrombotic therapy is an important morbidity in VTE patients. The reported bleeding risk in the Netherlands Registry was around 7% [62]. The risk for bleeding depends on patient-related factors (i.e., underlying disease, concomitant therapies, etc.) and antithrombotic therapy-related factors (i.e., type of therapy, dose and duration). Bleeding is estimated to occur in 20% of children during a therapeutic course of oral vitamin K antagonists and 17% receiving LMWH; using standard definitions "major" hemorrhage occurs in 2–4% [1]. The recommended management of antithrombotic therapy-induced bleeding depends on the type of therapy and severity and extent of bleeding [1].

VTE recurrence

The rate of DVT recurrence in children has been reported at 3.5% to 8% [41,61,62] at variable follow-up periods. In the Canadian registry the rate of recurrence was higher in older children [61]. In a single-center study, neither duration of enoxaparin therapy, nor quality of therapy (i.e., time of recommended anti-Xa levels of 0.5–1 IU/ml), were protective against recurrent DVT [66]. The impact of inherited thrombophilia on the risk of DVT recurrence in children was summarized in a systematic meta-analysis [67]. Recurrence was associated with all inherited thrombophilia traits except the factor V variant and elevated lipoprotein(a). Elevated D-dimer and factor VIII levels have also been associated with the development of a composite measure of poor outcome following VTE in children, in which recurrent VTE was a key component [73].

Post-thrombotic syndrome

Post-thrombotic syndrome is a syndrome of chronic venous insufficiency following DVT secondary to venous hypertension that develops as a result of venous valvular reflux, thrombotic veno-occlusion, or other causes of impaired venous return [68,69]. In a systematic review, the frequency of PTS following upper or lower extremity DVT was 26% (95% CI: 23–28%) among a total of nearly 1,000 children studied [70]. Individual studies have suggested that younger age, obesity, lack of thrombus resolution, number of vessels involved in the initial DVT, delayed initiation of anticoagulation, and elevated D-dimer and factor VIII levels are associated with development of PTS in children [70–73].

Adults who developed PTS had significantly worse quality of life (QoL) compared to those who did not develop PTS [74]. The QoL of patients with PTS was worse than in patients with other chronic diseases (e.g., chronic respiratory conditions and angina) and worse in patients with more severe PTS. No QoL data are available in children with PTS. Development of PTS in adults has been associated with an increased economic burden [75]. Again no pediatric data exist, but one might assume that this burden is even greater when PTS has earlier onset – i.e., in childhood.

Symptoms of PTS include persistent or intermittent swelling, aching pain, heaviness, cramps, itching or tingling in the affected limb and fatigue with exertion. Symptoms in the lower extremities may be aggravated by standing or walking and improve with resting, leg elevation and supine position [68]. Physical findings of PTS in the lower limb include edema, dilated superficial collateral veins, perimalleolar or more extensive telangiectasia, secondary varicose veins, brownish pigmentation of stasis dermatitis and venous eczema. Lipodermatosclerosis, brawny tender thickening of the subcutaneous tissues of the medial lower limb, may occur. In severe cases, venous leg ulcers, which can be precipitated by minor trauma, can occur and are generally chronic, painful and slow to heal. In the upper extremity, there may be dilation of the superficial veins of the upper arm and chest wall and dependent cyanosis of the arm.

The diagnosis of PTS is based on the development of characteristic symptoms and signs in a patient with prior DVT. Two main clinical scales for diagnosing and grading PTS were developed for children – the modified Villalta scale and the Manco-Johnson instrument [69,72]. In the modified Villalta scale, individual symptoms and signs are graded on a scale of 0–2. The symptom and sign scores are added together to