REVIEW ARTICLE

Venous thrombosis in children

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Summary. Venous thromboembolic (VTE) events are being increasingly diagnosed in systemic and cerebral vessels in children. Systemic VTE are increasing in children as a result of therapeutic advances and improved clinical acumen in primary illnesses that previously caused mortality. The epidemiology of systemic VTE has been studied in international registries. In children older than 3 months, teenagers are the largest group developing VTE. The most common etiologic factor is the presence of central venous lines. Clinical studies have determined the most sensitive diagnostic method for diagnosing upper system VTE are ultrasound for jugular venous thrombosis and venography for intrathoracic vessels. However, the most sensitive diagnostic methods for lower system VTE and pulmonary embolism (PE) have not been established. Treatment studies for VTE consist of inadequately powered randomized controlled trials or prospective cohort studies. The long-term outcome of systemic VTE, post-thrombotic syndrome, has been reported in children. Cerebral sinovenous thrombosis (CSVT) is becoming increasingly diagnosed in children due to the recognition of the associated subtle clinical symptoms and improved cerebrovascular imaging. The etiology of CSVT includes thrombophilia, head and neck infections, and systemic illness. Estimates of the incidence and outcome of childhood CSVT have recently become available through the Canadian Pediatric Ischaemic Stroke Registry. Clinical studies have not yet been carried out in children to determine the best method of diagnosis or treatment. There have only been case-series studies carried out in the treatment of CSVT. Properly designed clinical trials are urgently required in children with systemic VTE/PE and CSVT to define the best methods of diagnosis, treatment and long-term management.

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In memory of Dr Maureen Andrew, 1952–2001.

Introduction

Venous thromboembolic (VTE) events are increasing in children as a result of therapeutic advances in primary illnesses that previously caused mortality (congenital heart disease, malignancy, trauma). Teenagers and newborns are the largest groups developing VTE; however, events occur in all age groups of children. This report will discuss the epidemiology, diagnostic tests, congenital and acquired risk factors for VTE, long-term outcomes and antithrombotic therapy for the management of VTEs in children. Cerebral sinovenous thrombosis (CSVT) will be discussed separately. The report was completed following comprehensive MedLine reviews to identify all relevant publications. Aa number of areas were identified with deficiencies in data, including identification of safe and efficacious therapy and long-term outcome of VTE. The completion of properly designed trials is necessary to improve the care of children with VTE.

Systemic venous thromboembolic disease in children

Incidence

The estimated incidence of symptomatic VTE in children is significantly less than that in adults, 5.3/10 000 hospital admissions [1–7] vs. 2.5–5%, respectively [8–10]. Several mechanisms likely contribute to the protective effect of age for VTE. These include a reduced capacity to generate thrombin [11,12], increased capacity of α_2 macroglobulin to inhibit thrombin [13], and enhanced antithrombotic potential by the vessel wall [14,15]. However, increasing numbers of children are developing VTE as secondary complications to their underlying disorders; 95% of VTEs in children are secondary to serious diseases such as cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus (SLE) [4,16–18]. The role of congenital prothrombotic states in VTE remains con-

Table 1 Incidence, diagnosis, and treatment of non-central nervous system venous thrombosis

Type of thromboembolic event (TE)	Incidence	Diagnosis	Therapy (Recommendations are graded according to the supporting level of evidence)
Systemic venous TE	General population: 0.07 per 10 000 [2,4–7]	Upper venous system: Intrathoracic vessels venography sensitive [44] Neck vessels: US sensitive [154]	Treatment recommendations [123] LMWH [155]/UFH [117] (grade1C), duration of therapy (grade 2C). Warfarin is not recommended in children <12 months of age, except for mechanical heart valves [123]. (expert opinion). Thrombolytic therapy (tPA, rUK) is recommended for therapy only if potential loss of life, organ or limb due to high incidence of hemorrhage [138] (grade 2C)
Pulmonary embolism	High-risk populations: 1.7–32% [156]	V/Q scan [157], MRI/V, spiral CT, angiogram	As above, consider thrombolytic therapy or thrombectomy, if cardiorespiratory compromise (grade 2C)
Central venous line-related venous TE	Infants <1 years of age: 0–30% [155] Approx 35% in children: ALL [44],TPN [23], NS [22]	Upper venous system. Intrathoracic vessels: venography sensitivity [44] Jugular vessels: US [44]	Treatment: as above
Right atrial TE	No incidence data	Cardiac echogram	Treatment: as above, consider thrombectomy or thrombolytic therapy if cardiorespiratory compromise (grade 2C)
Post-thrombotic syndrome	12–62% [5,137]	Clinical diagnosis, outcome measure not validated [31]	No effective treatment. Custom-measured compression stockings may provide symptomatic relief [158] (grade 2C)

TE, Thromboembolic events; US, ultrasound; LMWH, low molecular weight heparin; tPA, tissue plasminogen activator; rUK, recombinant urokinase; V/Q scan, ventilation/perfusion scan; CT, computed tomography; TPNt, otal parenteral nutrition; NS, nephrotic syndrome.

troversial. Large family studies in patients with protein C, protein S, antithrmbin, factor (F) V Leiden and prothrombin gene defect found negligible rates of VTE in children <15 years of age [19]. However, cross-sectional, disease-oriented studies estimate the prevalence of congenital prethrombotic disorders in children with secondary VTE to be 13–78%, depending on the population of children studied [20]. The ages of greatest risk for VTE are in infants <1 year of age and teenagers [4,18]. Most children have several risk factors for VTEs with the most common risk factor being the presence of a central venous line (CVL). The most frequent non-CVL associated VTE is in the lower limb [4].

The incidence of CVL-related pulmonary embolism (PE) is unknown, and studies in the literature probably underestimate the incidence [6,21–24]. There are two cross-sectional studies using ventilation/perfusion (V/Q) scans to detect PE, reporting incidences of 12% and 28% in children requiring home total parenteral nutrition (TPN) and children with nephrotic syndrome, respectively [22,23]. Recurrent VTE has been estimated to occur in 6% of children with VTE [25].

Central venous line-related thrombosis

General information

Over 50% of VTEs in children occur in the upper venous system secondary to the use of central venous lines (CVLs) [4,18]. CVLs are placed for short-term intensive care, hemodialysis or long-term supportive care for children requiring TPN or therapy for cancer. CVL-related TEs are not trivial as they require repeat anesthesia for CVL placement, provide a source for PE [26,27], cause superior vena cava syndrome [26–28], chylothorax [26,27,29] and eventual destruction of the upper venous system [30], and contribute to post-thrombotic syndrome (PTS) in both upper and lower extremities [31]. Several mechanisms may play a role in the development of CVL-related VTE, including damage to the vessel wall by the CVL or by substances infused through the CVL (TPN, chemotherapy) [32,33], disrupted blood flow, and thrombogenic catheter materials [34]. Three types of CVL-related VTE are described in the literature; clots at the tips of CVLs, which impair infusion or withdrawal of blood, fibrin sleeves that are not adherent to vessel walls but may occlude CVLs [35], and CVL-related VTEs that adhere to vessel walls, with partial or complete obstruction of vessels in which the CVL is located [35].

Incidence

The incidence of CVL-related VTEs reported in the literature varies reflecting different underlying conditions, diagnostic tests, and index of suspicion. For example the incidence of CVL-related VTE in children receiving long-term TPN varies from 1% based on clinical diagnosis [36] to 35% based on ventilation perfusion scans or echocardiography, to 75% based on venography [30]. In two prospective cohort studies, 18% and 45% of children in an intensive care setting with CVLs in place for 48 h developed CVL-related VTE [37,38]. The recently completed PAARKA study reported an incidence of 37% venographically proven VTE in asymptomatic children with ALL receiving L-asparaginase therapy [39]. In

Table 2 IncIdence, diagnosis, and treatment of central nervous system thrombosis

Type of thromboembolic event (TE)	Incidence	Diagnosis	Therapy (Recommendations are graded according to the supporting level of evidence)
Cerebral venous TE	0.25/100 000 [58]	Angiography is the gold] standard [159] May also use: • MRI scanning with venography [159] • Doppler flow US; may be sensitive, if fontanelle open [159] • CT without contrast; has decreased sensitivity and specificity [58] • CT with contrast; has decreased sensitivity [58]	Four adult trials support anticoagulation therapy (grade 1C) Use of anticoagulants in children is controversial, probably not indicated in the presence of a large infarct or significant CNS hemorrhage [58] (grade 2C)
Complications of cerebral sinovenous thrombosis			
Mortality	2.5% [58]	–	–
Recurrence	17% [58]		
Seizures	11% [58]		
Neurologic deficit	39% [58]		

TE, Thromboembolic events; US, ultrasound; MRI, magnetic resonance imaging; CT, computed tomography; CNS, central nervous system.

many patient populations, the incidence is not accurately known.

Right atrial thrombosis

In children, there are no large prospective studies estimating the incidence of right atrial thrombosis (RAT), and reports in the literature associate the development of RAT with the presence of a CVL [36,40]. Clinically overt symptoms include cardiac failure, PE, loss of CVL patency, and persistent sepsis.

Clinical symptoms/complications

General information The clinical symptoms and complications of VTE can be classified as acute or long-term. The acute clinical symptoms include loss of CVL patency, swelling, pain, and discolouration of the related limb, swelling of the face and head with superior vena cava syndrome and respiratory compromise with PE. The long-term complications include prominent collateral circulation in the skin (face, back, chest, and neck as sequelae of upper venous VTE, and abdomen, pelvis, groin and legs as sequelae of lower venous VTE), repeated loss of CVL patency, repeated requirement for CVL replacement, eventual loss of venous access, CVL-related sepsis, chylothorax, chylopericardium, recurrent VTE necessitating long-term anticoagulation and its risk of bleeding, and PTS.

Post thrombotic syndrome Post-thrombotic syndrome is a serious long-term outcome of VTE consisting of pain, swelling, limb discoloration and ulceration resulting from damage to venous valves in deep vessels. The signs of PTS have been estimated to be present in up to 65% [31] of children post-VTE, but clinically significant PTS occurs in approximately 10–20% of children [5]. There is no properly validated outcome measure for PTS in children.

Upper venous system: central venous line-related VTEs

Asymptomatic

A well-designed substudy of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PAARKA) study compared venography vs. ultrasound for the diagnosis of asymptomatic upper venous system CVL-related VTE. Ultrasound was demonstrated to have a sensitivity of 20% for intrathoracic thrombosis, yet diagnosed jugular thrombi that were missed on venography [39].

Unlike the controversy in adults, radiographically detected asymptomatic CVL-related VTE in children are of clinical importance for a number of reasons. First, there is increasing evidence that CVL-related VTE are associated with CVL-related sepsis. In a meta-analysis, prophylactic unfractionated heparin (UFH) reduced CVL-related VTE (RR 0.43, 95% CI 0.23–0.78) and in addition decreased bacterial colonization (RR 0.18, 95% CI 0.06–0.60) and probably CVL-related bacteremia (RR 0.26, 95% CI 0.07–1.03) [41]. Second, CVL-related VTE are the most common source for PE in children [42], which may be fatal [6]. In children, PE is frequently not diagnosed during life due to subtle symptoms and the presence of primary illnesses that can cause sudden cardiorespiratory compromise. Third, the long-term sequelae of CVL-related VTE occurs in 10–20% [5,6] of children, destroying the underlying venous system and potentially limiting life-saving therapy because of the absence of venous access. Case reports have documented sudden death resulting from rupture of an intrathoracic vessel thought to be due to a previous CVL placement [43]. However, there are few studies and none currently support screening for VTE in any high-risk groups.

Recommendations Anticoagulation should be strongly considered, in the absence of contraindications (active bleeding, very high risk of bleeding) if an asymptomatic proximal VTE

is found during radiographic imaging completed for other reasons (diagnosis of malignancy, echocardiography to determine cardiac anatomy, cardiac catheterization) in an asymptomatic child.

Symptomatic The Determination of the Sensitivity and Specificity of Lineogram, Ultrasound and Venography in Children Symptomatic for VTE with Upper Venous System Central Lines (LUV) study [44] determined that most of the thrombi in this cohort were located in the jugular veins. In this cohort, the sensitivity of venography was poor, with ultrasound having 80% sensitivity for diagnosis of thrombi located in the jugular vessels.

Recommendations In a child who is symptomatic for VTE (pain, swelling or discoloration of an arm; or the CVL has altered patency), a chest X-ray should be performed to determine CVL position. If the CVL is in a good position and not fractured, ultrasound of the neck and intrathoracic vessels should be obtained. If the ultrasound is negative, and the clinical suspicion is high for VTE, the child should have a venogram of the intrathoracic vessels to rule out VTE.

Lower venous system central venous line-related VTEs

There are no studies determining the sensitivity and specificity of diagnostic testing for lower venous system CVL-related VTE in children.

Recommendations In a child who is symptomatic for VTE (pain, swelling or discoloration of an arm; or the CVL has altered patency) ultrasound can be used initially. If the ultrasound is negative, and the clinical suspicion is high for VTE, the child should have a venogram.

PE

There are no studies determining the sensitivity and specificity of diagnostic testing for PE in children.

Recommendations The following radiographic tests may be used to diagnose PE in children: ventilation perfusion scan, spiral CT, MRI, MRV or if possible, pulmonary angiogram.

Congenital prothrombotic disorders

General information

The contribution of congenital thrombophilia to childhood thrombosis remains controversial. The need to screen for prothrombotic disorders in children with major illnesses, undergoing an invasive procedure or confirmed thrombosis, especially in the presence of clinical risk factors, remains uncertain. In general, homozygous deficiency of antithrombin, protein C and protein S will present in the neonatal period and will not be further discussed.

FV Leiden

There is some evidence that FV Leiden homozygosity is associated with both primary and secondary VTE in children [45–51].

Prothrombin 20210A gene mutation

Most children with prothrombin gene mutation do not develop thrombosis until adult life [19].

Hyperhomocysteinemia

Excessive plasma levels of homocysteine due to homozygous deficiencies of enzymes such as cystathione β synthase or methylenetetrahydrofolate reductase may be associated with severe VTE in children [52,53].

Lipoprotein A

Increased plasma levels of lipoprotein (a) in children have been reported in cohorts of children with VTE [54].

Acquired prothrombotic disorders

Nephrotic syndrome

The reported incidence of thrombosis in children with nephrotic syndrome is dependent upon the diagnostic method used and is at least 10% when using objective radiographic methods [55].

Antiphospholipid antibody syndrome

An association between antiphospholipid antibodies (APLAs) and VTE in children exists. The incidence of VTE in children with SLE ranges from 21 to 57% [16,17,56,57]. The prevalence of APLAs in children with or without SLE is reported to be 25% [16].

Cerebral VTEs in children: stroke

Introduction

Cerebral sinovenous thrombosis (CSVT) is increasingly recognized in children; however, clinical trials have not been conducted to date. An understanding of the incidence, risk factors and outcomes is important, since these will enable the development of clinical trials assessing selected therapies to reduce the adverse outcomes. This review will focus on CSVT occurring in the young infant and child, and excludes neonatal CSVT.

Incidence

Estimates of the incidence of childhood CSVT have recently become available. In the Canadian Pediatric Ischaemic Stroke Registry, the incidence of childhood CSVT was 0.67 per

100 000 per year, with non-neonates comprising 57% of children, yielding a minimum incidence of 0.25 per 100 000 older infants and children per year [58].

Neurologic presentation

The clinical features of childhood CSVT are subtle, diffuse and dominated by seizures. Signs of raised intracranial pressure typically develop gradually over hours, days or even weeks. The clinical presentation is influenced by the age of the child, the extent and location of the thrombus, and the presence or absence of associated venous infarction.

In children, the most frequent neurologic signs of CSVT are diffuse neurologic signs, present in 90%, including headache, decreased level of consciousness and papilledema, and seizures, present in 48%. Hemiparesis is present in only 17% [58]. The clinical presentation may be indistinguishable from pseudotumour cerebri: CSVT has been found in 25% of children and adults with pseudotumour cerebri undergoing angiography or MRV [59,60]. Visual disturbances, present in 18% include diplopia, increased central scotoma or other visual field deficits.

Risk factors

In childhood CSVT, thrombosis results from a combination of intravascular and vascular factors. Underlying risk factors including prothrombotic states may 'predispose' to thrombosis, while acute illnesses or prothrombotic medications act as 'triggering' factors. Only 3% of children in the Registry had 'idiopathic' CSVT compared with an estimated 10–25% of adults. Pregnancy [61], malignancy [61,62], and exogenous steroids, frequently associated with CSVT in adults, are only rarely found in children with CSVT [63].

Head and neck infections resulting in 'septic' CSVT, present in 23% of older infants and children, are particularly common in preschool children and are related to otitis media and mastoiditis [58]. Head trauma or cranial surgery may damage dural sinuses triggering CSVT. In approximately 60%, chronic systemic disease, including SLE, nephrotic syndrome, inflammatory bowel disease, hematologic disorders, underlying cardiac disease and others, are an underlying risk factor [58,64,65]. Acute illnesses including sepsis or dehydration are present in nearly one third of children with CSVT. In older infants iron deficiency anemia may underlie CSVT [66].

Prothrombotic disorders are reported in 33–96% of children with CSVT, the latter figure representing children with otherwise idiopathic CSVT. This contrasts with their reported frequency in adults with CSVT of 15–21% [67,68]. Congenital prothrombotic disorders including FV Leiden, prothrombin gene G20210A, dysfibrinogenemia, deficiencies of protein C, protein S and antithrombin, FXII deficiency, increased FVIII, and a thrombomodulin mutation have all been reported, however, they are relatively rare [69–78].

Acquired prothrombotic states may be multiple in individual children and are more frequently found. The latter include anticardiolipin antibody, lupus anticoagulant, acquired activated protein C resistance, acquired deficiencies of protein C, protein S, and antithrombin and hyperhomocysteinemia [72,79–81]. However, the role of acquired prothrombotic abnormalities in the causation of CSVT is still being explored.

Radiographic features

There are frequently multiple sites of obstruction within the cerebral sinovenous structures in children at the time of diagnosis. The most frequently involved are the lateral (including transverse and sigmoid) sinuses and the superior sagittal sinus, the major components of the 'superficial' sinus system. Cortical vein thrombosis is present in 9%. The 'deep' sinovenous system including the vein of Galen, straight sinus and internal cerebral veins, is involved in 36%. Jugular veins are involved in 14%. Cavernous sinus thrombosis has been reported in children from Thailand [82] and India [83], but rarely reported in North American or European series.

Nearly 41% of children with CSVT have associated parenchymal infarcts. In the Canadian Registry, these were bland in 43% and hemorrhagic in 57% [58]. Transient focal edema can mimic venous infarction. With extensive CSVT, diffuse cerebral swelling results from venous outflow obstruction and, in sagittal sinus thrombosis is compounded by a communicating hydrocephalus due to impaired absorption of cerebrospinal fluid into the arachnoid granulations that line the sagittal sinus.

Diagnostic tests

The diagnosis of CSVT requires either imaging the thrombus within sinovenous channels, or a reduction or obliteration of venous flow within venous sinuses.

Computed tomography scanning Computed tomography (CT) scanning can demonstrate large occlusive thrombus as an area of increased density on a non-contrast-enhanced scan, or as low density due to lack of contrast filling on a contrast-enhanced scan. However the location of the venous sinuses adjacent to the bony skull, combined with the 'bone artefact' on CT scans can result in missed diagnosis in more subtle cases [60]. In the absence of good coronal images, it can be difficult to distinguish subdural hemorrhage along the edges of the tentorium cerebelli from intraluminal thrombus in the transverse or sigmoid sinus. High-resolution CT with contrast enhancement can detect bony changes in the mastoid in children with lateral sinus thrombosis suspected to have mastoiditis.

CT venography using multi-slice technique is superior to CT and is viable alternative to MRI and MRV [59,84–87]. However, issues of radiation dose with CT in children have become more prominent as its use has increased.

Magnetic resonance imaging Magnetic resonance imaging with venography is the most sensitive and specific test because of its capacity to visualize flow, the presence of thrombus, and associated cerebral infarct [59,84–88]. However on spin echo MR images, the diagnosis of CSVT can be complex, since both

thrombi and flow can produce overlapping signal intensities. Recently 3D gadolinium-enhanced MRV techniques have become popular [80]. One modification of MR is a dynamic gadolinium bolus-injection technique in which the acquisition of images is triggered by the arrival of the gadolinium bolus at the vessel of interest. The latter technique images the dural venous sinus system and compared well with conventional angiography [89].

Ultrasound In young infants the presence of an open fontanelle can allow the opportunity for non-invasive and inexpensive ultrasound methods of imaging the brain and sinovenous system. Power Doppler appears to be superior to conventional colour Doppler in assessing for CSVT [90].

Conventional angiography During the last decade, the use of diagnostic angiography has fallen dramatically. In the Canadian Registry, fewer than 10% of children underwent conventional angiography [58]. However, in cases in which other modalities do not demonstrate CSVT, angiography may be required. Classic angiographic findings are similar to those in adults with CSVT and include partial or complete lack of filling of cerebral veins or sinuses, enlarged collateral veins, delayed venous emptying, reversal of normal venous flow direction, abnormal cortical vein (broken or corkscrew-like), and regional or global delayed venous flow [59].

Neurologic outcome

The majority of children (90%) with CSVT survive the initial illness. Deaths are attributable to the CSVT in approximately one-quarter of patients who die. In the Canadian Registry, outcomes were assessed in 82 older infants and children at a mean interval from thrombosis to the last follow-up visit of 1.6 years (range 0.05–5.2). There were 42 (51%) with normal outcome, 32 (39%) with neurologic deficits, and 8 (10%) who died, two as a consequence of the CSVT. Other outcomes in the Registry included seizures in 11% and recurrent VTEs in 17%. Predictors of adverse neurologic outcome or death in the Registry included seizures at onset and presence of a venous infarct. Although neurologic deficits are present in one-quarter of the children, deficits impacting on neurologic function occur in about 20% [91]. Long-term follow-up of affected children is very important, since the onset of signs of neurologic injury is delayed in this age group.

Antithrombotic therapy in children

Heparin therapy in pediatric patients

Mechanism of action The anticoagulant activities of heparin are mediated by catalysis of antithrombin. Some pediatric patients requiring heparin therapy have very low levels of antithrombin reflecting physiologic, congenital and/or acquired etiologies. These levels may impair the function of therapeutic heparin.

At heparin concentrations in the therapeutic range, the capacity of plasma to generate thrombin is delayed and decreased by 25% in children, compared with adults [12,92]. Optimal dosing of heparin will likely differ in pediatric patients from adults. However, to date there are no clinical studies to confirm this hypothesis.

Therapeutic range The recommended therapeutic range for the treatment of VTEs in adults (and by extrapolation, children) is an activated partial thromboplastin time (APTT) that reflects a heparin level by protamine titration of $0.2–0.4\,U\,mL^{-1}$ or an anti-FXa level of $0.35–0.7\,U\,mL^{-1}$ [93]. In pediatric patients, APTT values correctly predict therapeutic heparin concentrations approximately 70% of the time [94].

Doses The doses of heparin required in pediatric patients to achieve adult therapeutic APTT values have been assessed using a weight-based nomogram (one prospective cohort study) [94]. Bolus doses of $75–100\,U\,kg^{-1}$ result in therapeutic APTT values in 90% of children (unpublished data). Maintenance heparin doses are age-dependent, with infants having the highest requirements ($28\,U\,kg^{-1}\,h^{-1}$) and children over 1 year of age having lower requirements ($20\,U\,kg^{-1}\,h^{-1}$). The doses of heparin required for older children are similar to the weight-adjusted requirements in adults ($18\,U\,kg^{-1}\,h^{-1}$) [95].

Heparin-bonded catheters Heparin-bonded catheters can potentially be used as primary prophylaxis to prevent CVL-related VTE [96].

Adverse effects There are at least three clinically important adverse effects of heparin. One cohort study reported bleeding in 1.9% (95% CI 0.1–10.2%) of children being treated for VTE [94]. However, many children were treated with suboptimal amounts of heparin (compared with target APTT) in this study [94], and further studies are required to determine the true frequency of heparin induced bleeding in children. There are only three case reports of pediatric heparin-induced osteoporosis, two of whom received concurrent steroid therapy [97–99]. The third received high-dose intravenous heparin therapy for a prolonged period [98]. However, given the convincing relationship between heparin and osteoporosis in adults, long-term use of heparin in children should be avoided when other alternative anticoagulants are available. There have been a number of case reports of pediatric heparin-induced thrombocytopenia (HIT) in the literature, ranging in age from 3 months to 15 years [100–105]. Recent studies suggest the frequency of HIT may be increased in children in intensive care (2.3%) compared with children in a non-intensive care setting [106,107]. A high index of suspicion is required to diagnose HIT in children, as many patients in neonatal or pediatric intensive care units who are exposed to heparin have multiple reasons for thrombocytopenia and/or thrombosis. Danaparoid, hirudin and argatroban are alternatives to heparin in children with HIT [100,102,105,108,109].

Low molecular weight heparin therapy in pediatric patients

The potential advantages of low molecular weight heparin (LMWH) for children include the need for minimal monitoring (important in pediatric patients with poor or non-existent venous access); lack of interference by other drugs or diet such as exists for warfarin; reduced risk of HIT; and probable reduced risk of osteoporosis with long-term use compared with heparin.

Therapeutic range Therapeutic doses of LMWH are extrapolated from adults and are based on an anti-FXa levels. The guideline for therapeutic LMWHs is anti-FXa level of 0.50–1.0 U mL^{-1} in a sample taken 4–6 h following a subcutaneous injection. Anti-FXa levels reflect the pharmacologic concentration of the LMWH but do not accurately reflect its antithrombotic activity [110].

Doses The doses of LMWH required in pediatric patients to achieve adult therapeutic anti-FXa levels have been assessed for enoxaparin, reviparin, dalteparin and tinzaparin [111–114].

In general, peak anti-FXa levels occur 2–6 h following a subcutaneous LMWH injection. Children less than approximately 2–3 months of age or <5 kg have increased requirements per kg, probably due to a larger volume of distribution. Alternative explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics [112,115] and/or a decreased expression of anticoagulant activity of heparin in children due to decreased plasma concentrations of antithrombin [116].

Adverse events In a single institution cohort study of 146 courses of therapeutic enoxaparin, major bleeds occurred in 4.8% (95% CI 2–9.6%) of patients [117]. In a randomized trial ($n = 37$) of reviparin, major bleeding occurred in 8.1% (95% CI 1.7–21.9%) [25]. There are no data on the frequency of HIT or osteoporosis secondary to LMWH use in children.

Treatment of LMWH-induced bleeding Equimolar concentrations of protamine sulfate neutralize the anti-FIIa activity but result in only partial neutralization of the anti-FXa activity [118]. However, in animal models, bleeding is completely reversed by protamine sulphate [119–122]. The dose of protamine sulfate is dependent on the dose of LMWH used at the time of administration. Protocols for reversal have been published [123].

Oral anticoagulant therapy in pediatric patients

Age dependent features For children receiving oral anticoagulants, the capacity of their plasmas to generate thrombin is delayed and decreased by 25% compared with plasmas from adults with similar International Normalized Ratios (INRs) [124]. The latter raises the issue of whether the optimal INR therapeutic range for children will be lower than for adults. This hypothesis is further supported by the observation that plasma concentrations of a marker of endogenous thrombin generation, prothrombin fragment 1.2, is significantly lower in children compared with adults at similar INR values [124].

Therapeutic range Currently, therapeutic INR ranges for children are directly extrapolated from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children based upon clinical outcomes.

Dose–response An initial dose of 0.2 mg kg^{-1}, with subsequent dose adjustments made according to a nomogram using INR values, was evaluated in a prospective cohort study [125]. The published age-specific weight-adjusted doses for children vary due to the different study designs, patient populations and possibly the small number of children studied. The largest cohort study ($n = 263$) found infants required an average of 0.33 mg kg^{-1} and teenagers 0.09 mg kg^{-1} warfarin to maintain a target INR of 2–3 [126]. For adults, weight adjusted doses for oral anticoagulants are not precisely known but are in the range of 0.04–0.08 mg kg^{-1} for an INR of 2–3 [127]. The mechanisms responsible for the age dependency of oral anticoagulant doses are not completely clear.

Monitoring Monitoring oral anticoagulant therapy in children is difficult and requires close supervision with frequent dose adjustments [125,128]. In contrast to adults, only 10–20% of children can be safely monitored monthly [125]. Reasons contributing to the need for frequent monitoring include diet, medications, and primary medical problems. Breast-fed infants are very sensitive to oral anticoagulants due to the low concentrations of vitamin K in breast milk [129–132]. In contrast, some children are resistant to oral anticoagulants due to impaired absorption; requirements for TPN, which is routinely supplemented with vitamin K, and nutrient formulae, which are all supplemented with vitamin K (55–110 μg L^{-1}) to protect against hemorrhagic disease of the newborn [132, 133, 140].

Whole-blood monitors for children Whole-blood monitors use various techniques to measure the time from application of fresh samples of capillary whole blood to coagulation of the sample, and report an INR value. Point-of-care monitors evaluated in children were shown to be acceptable and reliable for use in the outpatient laboratory and at home settings [134,135].

Adverse effects of oral anticoagulants Bleeding is the main complication of oral anticoagulants. The risk of serious bleeding in children receiving oral anticoagulants for mechanical prosthetic valves is less than 3.2% per patient-year (13 case series) [123]. In one large cohort (391 warfarin years, variable target range) bleeding rate was 0.5% per patient-year [128]. In a randomized trial ($n = 41$) target range 2–3 for 3 months, bleeding occurred in 12.2% (95% CI 4.1–26.2) [25].

Non-hemorrhagic complications of oral anticoagulants, such as tracheal calcification or hair loss have been described on rare

occasions in young children [136]. A cohort study has described reduced bone density in children on warfarin for greater than 1 year. However, this was an uncontrolled study, and the role of the underlying disorders in reducing bone density remains unclear [137].

Alternative antithrombotic therapy in children

Thrombolytic agents are used commonly for arterial thrombosis in children, and to unblock CVLs. The role of thrombolysis in the treatment of VTE is controversial. Potential indications are obstructive intracardiac thrombosis, massive PE, bilateral renal vein thrombosis, acute organ dysfunction due to massive thrombosis [138].

There are an increasing number of antithrombotic agents used in adults, the majority of which have been tested in large clinical trials. However there are only limited data on these drugs in children. Danaparoid, hirudin, and argatroban have been used in children [100,102,105,108,109,111,139,140].

In addition to pharmacologic therapy, venous interruption devices (inferior vena cava filters) are used for specific clinical indications in adults. The most common indication for the use of inferior vena cava interruption is to prevent PE in the presence of a contraindication to anticoagulant therapy, or in a patient with a high risk of proximal deep venous thrombosis (DVT) [141–143]. There is limited experience in children, however, temporary filters are more often used and removed when the source of PE is no longer present [144,145]. The risk–benefit ratio needs to be considered individually in each case.

Surgical embolectomy is rarely used for venous thrombosis in children. Surgical embolectomy may be considered for massive obstructive thrombosis; however, experience with this procedure in children is limited.

Guidelines for antithrombotic therapy

The following guidelines for antithrombotic therapy in children are graded according to the level of evidence supporting each recommendation. The grading is based on estimate of risk and benefit and the methodologic strength of the studies supporting the recommendation. Grade 1 and grade 2 recommendations differ in that the estimate of risk and benefit associated with each approach is either clear or unclear, respectively. The methodologic strength of the study(ies) providing support for the recommendation is then graded as either A, B or C. Grade A and B represent randomized trials without or with important limitations, respectively. Grade C represents observational studies [123].

Non-central nervous system VTE events

First thromboembolic event Children (over 2 months of age) with an initial VTE should be acutely treated with intravenous (i.v.) UFH sufficient to prolong the APTT to a range that corresponds to an anti-FXa level of $0.35–0.7\,U\,mL^{-1}$; or

LMWH sufficient to achieve an anti-FXa level of $0.5–1.0\,U\,mL^{-1}$ 4 h after an injection (grade 1C +) [123].

Initial treatment with heparin or LMWH should be continued for 5–10 days. For patients in whom subsequent oral anticoagulant therapy will be used, it can be started as early as day 1 and heparin/LMWH discontinued on day 6 if the INR is therapeutic on two consecutive days [123]. For massive PE or extensive VTE a longer period of heparin or LMWH therapy should be considered (grade 1C+) [123].

Patients with a first episode of idiopathic venous thromboembolism should be treated with anticoagulant agents for longer than 3 months using oral anticoagulants to achieve a target INR of 2.5, range 2.0–3.0; or alternatively LMWH to maintain an anti-FXa level of $0.5–1.0\,U\,mL^{-1}$ (grade 2C) [146].

In the presence of an inherited thrombophilic disorder and a positive family history for thrombosis, consideration should be given to lifelong anticoagulation (grade 2C) [147].

For secondary VTE, anticoagulant therapy should be continued for at least 3 months using oral anticoagulants to achieve a target INR of 2.5, range 2.0–3.0; or alternatively LMWH to maintain an anti-FXa level of $0.5–1.0\,U\,mL^{-1}$ (grade 2C) [123].

In the presence of ongoing risk factors, such as active nephrotic syndrome, or a lupus anticoagulant, anticoagulant therapy should continue until the risk factor has resolved (grade 2C) [123]. The optimal intensity of therapy, therapeutic or prophylactic is controversial.

Recurrent VTE event For recurrent idiopathic VTE, following the initial treatment (longer than 3 months) indefinite therapy with either therapeutic or prophylactic doses of oral anticoagulants or LMWH may be used (grade 2C) [123].

For recurrent secondary VTE, following the initial 3 months of therapy, anticoagulation therapy should be continued until removal of any precipitating factors (grade 2C) [123].

Central venous line-related thrombosis

There are two aspects to the management of CVL-related VTE: first, management of the CVL itself, and second, anticoagulation therapy.

If the CVL is no longer required, or is non-functioning, it should be removed. (grade 2C) In general, a period (3–5 days) of anticoagulation prior to removal is preferred, especially if there is a known right to left shunt. If CVL access is required and the CVL involved is still functioning, then the CVL can remain *in situ* (expert opinion) [123].

Anticoagulation therapy should be given as described for any first VTE (grade 1C+) [123].

Following the initial 3 months of therapy, for children with a first CVL-related DVT, prophylactic doses of oral anticoagulants (INR 1.5–1.8) or LMWH (anti-FXa levels of 0.1–0.3) are options until the CVL is removed (grade 2C) [123].

For recurrent CVL-related VTE, following the initial 3 months of therapy, prophylactic doses of oral anticoagulants (INR 1.5–1.8) or LMWH (anti-FXa levels of 0.1–0.3) should be

continued until removal of the CVL. If the recurrence occurs while on prophylactic therapy, therapeutic doses should be continued until the CVL is removed or for a minimum of 6 months (grade 2C) [123].

Sinovenous thrombosis

Anticoagulant therapy in children with cerebral sinovenous thrombosis (CSVT) is controversial. Data from several clinical trials have demonstrated the efficacy and safety of heparin in adults with CSVT [148–150]. In the past decade in the Canadian Pediatric Stroke Registry, 60 of 91 (66%) older infants and children were selected for anticoagulant therapy with UFH or LMWH and warfarin. There were no treatment-related deaths or major hemorrhagic complications.

In the absence of major central nervous system (CNS) hemorrhage, anticoagulation is appropriate. Anticoagulation therapy is given for 3 months if full recanalization is seen on the 3-month monitoring CT venogram or MRV study, or 6 months if only partial recanalization is seen on the 3-month monitoring CT venogram or MRV study. A similar dose intensity (target INR 2.0–3.0) is utilized as that described for non-CNS venous thrombosis. The latter treatment duration is consistent with the treatment approach for adult CSVT. Small petechial or localized hemorrhage confined to an area of venous infarction may not be a contraindication to anticoagulation. If no anticoagulants are given (e.g. significant hemorrhage) repeat MRV or CT venogram should be obtained at 1 week after diagnosis to assess for propagation of the initial thrombosis. Discussion with a hematologist or neurologist experienced in managing such problems is recommended (grade 2C) [123,148,149,151].

Primary prophylaxis for VTE in children

In general, primary prophylaxis for children with CVLs cannot be recommended at this time, because there is no evidence for the efficacy or safety of this approach. However, children having long-term home TPN may benefit from antithrombotic prophylaxis (grade 2C) [30,123].

Short-term prophylactic anticoagulation is an option for children with known congenital prothrombotic disorders, strong family history of thrombosis who are in high-risk situations such as immobility, significant surgery or trauma and have multiple (three or more) acquired risk factors (grade 2C) [123]. The risk benefit ratio needs to be considered for each individual patient. The optimal prophylactic regimen in this situation is unknown; however adult studies have used fixed low dose warfarin (1 mg day^{-1}) or prophylactic doses of dalteparin [152,153].

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