PEDIATRIC VENOUS THROMBOEMBOLISM

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PEDIATRIC VENOUS THROMBOEMBOLISM

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Venous thromboembolism (VTE) occurs less often in children than adults and therefore remains underrecognized despite increasing in incidence. Due to the risk of mortality, short- and long-term morbidity, and increased healthcare costs associated with pediatric VTE, this entity merits better understanding and consideration. With this Research Topic, we aim to highlight some special considerations of pediatric VTE, namely risk factors and epidemiology, rare types of pediatric thrombosis and considerations unique to specific clinical patient subgroups, approaches to management and treatment, and prevention.

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EDITORIAL
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Editorial: Pediatric Venous Thromboembolism

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Editorial on the Research Topic

Pediatric Venous Thromboembolism

Due to the morbidity, mortality, and healthcare costs of venous thromboembolism (VTE), the focus on its treatment and prevention is growing steadily. As part of a response to the U.S. Surgeon General's 2008 call-to-action to prevent VTE (1), the Healthy People 2020 initiative included a goal to reduce the number of people who develop a VTE by at least 10% (2). The American Society of Hematology recently emphasized its focus on transforming VTE care and updated its research agenda to prioritize studies that increase understanding of VTE risk profiles based upon unique pathophysiologic mechanisms in specific clinical subgroups of patients and assess the safety and efficacy of various prevention strategies (3). Similarly, the National Heart, Lung, and Blood Institute at the National Institutes of Health includes in a recent publication of its strategic vision a focus on identifying factors that account for individual differences in VTE pathobiology and in responses to treatments (4).

The incidence of VTE in pediatric patients is increasing (rising by 70% in under a decade) (5), but the body of medical literature surrounding this topic is not keeping pace. This trend is most dramatic in hospitalized children (averaging 5–22 per 10,000 pediatric inpatients) (6–9), but community-acquired pediatric VTE is also increasing (0.1–0.5 per 10,000 children) (7, 8). The Children's Hospitals Solutions for Patient Safety collaborative recently determined that that hospital-acquired VTE is the second-largest cause of preventable harm in approximately 130 pediatric hospitals participating in this network (10, 11). VTE is associated with catastrophic short term complications, including pulmonary embolism in 15–20% (12) which confers a mortality rate of nearly 10% (13). Long term complications also occur, such as recurrent VTE or post-thrombotic syndrome (chronic pulmonary hypertension or painful limb swelling secondary to venous insufficiency) in 20% of cases (14). Finally, an episode of pediatric VTE can cost the healthcare system nearly $30,000, not only by increasing length of hospitalization by an average of 8 days, but also by creating a need for additional outpatient visits, extended drug treatment costs, and the potential for additional testing to investigate inherited or acquired thrombophilia (15–17). Drug treatment costs are likely to increase as the use of more expensive direct oral anticoagulants rises in children after ongoing dose-finding studies are completed. In response to the rising burden imparted by this disease, we designed this article collection to highlight pediatric-specific VTE risk factors, diagnosis, and treatment strategies, guidelines for risk assessment, risk-based prevention efforts, and education for the medical community about this serious, sometimes overlooked, medical condition in children.

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The purpose of this Research Topic, comprising 16 articles by 35 authors, is to provide a comprehensive survey of the myriad considerations within pediatric VTE. We have welcomed worldwide thrombosis experts to write about epidemiology and risk assessment of pediatric VTE. Other specific topics include hospital-acquired VTE, community-acquired VTE, thrombosis in acutely ill children, neonates, adolescents, and those with high-risk medical issues such as cancer or congenital heart disease or specific risk factors such as central venous catheters, inherited thrombophilia, inflammation, critical illness, and trauma. Additionally, we have highlighted thrombosis in specific anatomic locations with unique diagnostic and management consideration, including abdominal veins, pulmonary embolism, and cerebral sinovenous thrombosis, as well as vascular anomalies. This Research Topic also addresses treatment for VTE in children, such as systemic and catheter-directed thrombolysis, as well as the various new oral direct-acting anticoagulants (many of which are expected to gain FDA approval for pediatrics in the coming years), for which few written guidelines exist.

Though pediatric VTE has long suffered from a paucity of high-quality evidence from which to derive practice standards and treatment/prevention guidelines, some articles in this Research Topic highlight key ongoing studies that aim to increase our knowledge in this area. One such study, mentioned in the pulmonary embolism (Zaidi et al.) and VTE treatment (Malec and Young) articles, is the Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT) study that aims to determine the optimal duration of treatment (6 weeks vs. 3 months) for children with provoked deep vein thrombosis (18). Similarly, the Children's Hospital-Acquired Thrombosis registry study (19), a multi-institutional effort to retrospectively derive a pediatric VTE risk-assessment model for subsequent prospective validation, is discussed in the epidemiology/risk assessment article by Mahajerin and Croteau.

Overall, we feel this Frontiers in Pediatrics Research Topic is a unique opportunity to highlight this important topic in a single pediatric-specific resource.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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MINI REVIEW
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Epidemiology and Risk Assessment of Pediatric Venous Thromboembolism

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The incidence of diagnosed venous thromboembolism (VTE) has been increasing concurrent with advances in technology and medical care that enhance our ability to treat pediatric patients with critical illness or complex multiorgan system dysfunction. Although the overall incidence of VTE is estimated at 0.07–0.49 per 10,000 children, higher rates are observed in specific populations including hospitalized children, those with central venous catheters (CVCs) or patients convalescing from a major surgery. While the absolute number of pediatric VTE events may seem trivial compared to adults, the increasing incidence, associated with increased mortality and morbidity, the availability of novel therapies, and the impact on the cost of care have made investigation of VTE risk factors and prevention strategies a high priority. Many putative risk factors for pediatric VTE have been reported, primarily from single-institution, retrospective studies which lack appropriate methods for verifying independent risk factors. In addition, some risk factors have inconsistent definitions, which vex meta-analyses. CVCs are the most prevalent risk factors but have not consistently been assigned the highest level of risk as defined by odds ratios from retrospective, case–control studies. Few risk-assessment models for hospital-acquired pediatric VTE have been published. Some models focus exclusively on hospitalized pediatric patients, while others target specific populations such as patients with cancer or severe trauma. Multicenter, prospective studies are needed to identify and confirm risk factors in order to create a pediatric risk-assessment tool and optimize preventive measures and reduce unintended harm.

Keywords: epidemiology, pediatrics, thrombosis, risk factors, risk assessment

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INTRODUCTION

Understanding and intervening on preventable factors that provoke venous thromboembolism (VTE) in pediatrics is a leading initiative for children's hospitals (1). As the second leading cause of hospital-acquired morbidity (preventable harm) for children in the U.S., VTE significantly increases hospitalization costs. Using the nationwide inpatient sample, one recent analysis estimated increased mean hospital costs of $27,686 and mean length of stay (LOS) extension of 8.1 days in children with hospital-acquired VTE (HA-VTE) compared to controls (2).

The foundation of our current knowledge of pediatric VTE has emerged primarily through registries, administrative databases, and retrospective cohort studies (3–8). Differences in the patient population included and analysis make comparison of these studies challenging. The relative

contributions of genetic, anatomic, and acquired risk factors in pediatrics have been less studied than in adults (9, 10). Sequelae of VTE, namely post-thrombotic syndrome (PTS) and recurrence risk, have not been fully investigated in children, but efforts to standardize outcome measures are underway (11–13). This pediatric VTE compendium contains mini-reviews on VTE in the setting of cancer, congenital heart disease, inflammatory states, central venous catheters (CVCs), trauma, and thrombophilia. This mini-review will focus on epidemiology of pediatric VTE as well as patient and acquired risks. For additional discussion of pediatric VTE in a specific disease or clinical state, see the accompanying mini-reviews.

INCIDENCE

The estimated incidence of pediatric VTE in developed countries ranges from 0.07 to 0.49 per 10,000 children (3, 14). VTE rates are notably higher in hospitalized children, 4.9–21.9 per 10,000 hospital admissions (3, 14, 15). A bimodal distribution is evident. The most prominent peak is in early infancy accounting for up to 20% of pediatric VTE. A second peak occurs during adolescence with about 50% of VTE events occurring in children 11–18 years old. Reported incidence rates vary due to differences in study design, cohort inclusion criteria (e.g., all events versus symptomatic events, whether neonates are included, and/or if age-specific sub-analyses are performed), whether the source of information is a database based on billing codes or whether radiological confirmation was required for inclusion. For example, VTE incidence rates in the Netherlands decreased from 0.14 per 10,000 children to 0.05 per 10,000 children when neonates and non-extremity VTE events were excluded (8).

While the annual burden of thrombosis is greater in adults (5.6–16 per 10,000 adults per year) (9, 16), the rate of increase in observed incidence in children discharged from tertiary care hospitals is notable. Cohort studies targeting HA-VTE demonstrate a steep rise in incidence, increasing from 0.3 to 28.8 cases per 10,000 admissions (1992–2005) in one study and from 34 to 58 cases per 10,000 admissions (2001–2007) in another (17, 18). In contrast to the majority of studies focused on hospital-based populations, longitudinal data from a population-based cohort study in Québec, QC, Canada found a stable VTE incidence of 0.29 events per 10,000 person-years in children less than 18 years old over the 11-year study period ending in 2004 (5). Notably, this study excluded patients less than 1 year of age, and rates were calculated based on person-years, as opposed to VTE rate per hospital admissions.

The majority of VTE diagnosed in children arise proximal to hospitalization and are considered *provoked*. At least one risk factor is identified in the majority of patients (19–21). This stands in contrast to adults where 30–50% of VTE events are idiopathic or spontaneous. CVC-associated VTE predominates in pediatrics. In the absence of a CVC, however, location frequency of VTE varies by age group. Renal vein VTE comprises a significant proportion of events in neonates but is exceedingly rare in older children where lower extremity VTE is more likely. Although rare, non-extremity VTE in children may arise in portal, splenic, mesenteric, pulmonary vessels, or cerebral sinuses (22). No racial or ethnic variations have been described, and data on gender differences are conflicting.

Pediatric subpopulations have higher VTE incidence including children with critical illness, neoplasm, renal disease (nephrotic syndrome), congenital heart disease, inflammatory bowel disease, or obesity and neonates. Children admitted to the intensive care unit (ICU) have a 2% higher risk of VTE if they had a short-term CVC and LOS greater than 7 days (23). Occurrence of VTE in neonates has been estimated as high as 24 per 10,000 neonatal intensive care admissions (20). There are presently no standard thromboprophylaxis guidelines to mitigate increased VTE risk.

RISK FACTORS

Many patient attributes, medical diagnoses, and elements of hospitalized care have been shown or suggested to confer HA-VTE risk. Risk factor data are predominately derived from single-institution, retrospective cohort, or case–control studies (10).

Immobility

Absence of consensus on terms *altered mobility* versus *immobility* creates a challenge when attempting to define the associated risk of these states and potential risk reduction with intervention. Data from adults show a strong association with various etiologies of immobility, e.g., post-surgery, plaster cast. Altered mobility without immobilization also increases risk of symptomatic DVT but to a lesser extent than chronic immobilization (24, 25). Wells' criteria for suspected DVT have "recently bedridden for 3 days or more" in their clinical model (26). The benchmark of 3 days or more has previously been suggested to confer a high degree of risk in pediatrics but has not been prospectively studied (27). Multiple studies have implicated altered mobility as a risk factor for pediatric HA-VTE. Unfortunately, the granularity to understand and compare duration or degree of altered mobility among studies is lacking (10).

The Braden Q mobility assessment offers a guide for grading mobility (28); however, HA-VTE risk has not been clinically correlated to a threshold score. Prospective evaluation of mobility rubrics in both children and adults is needed to determine VTE risk associated with different mobility states.

Infection

Infection is often cited as a risk factor without descriptors of location, extent, severity, or inciting organism (29, 30). Occasionally, a specified set of infectious conditions (e.g., meningitis, bacteremia) are categorized as "infection" (31), or infection is dichotomized to focal or systemic. Systemic infections are thought to confer higher risk than a focal infection, but this may depend on location. For example, otitis media or mastoiditis are considered "focal" infections and associated with increased risk of cerebral sinus venous thrombosis (32). Similarly, acute osteomyelitis has been noted to increase risk of VTE in adjacent veins (33). Evaluation of different infectious events and reporting confirmation, e.g., culture, is needed to understand VTE risk of focal and systemic infections. Concomitant inflammation likely

plays a role but may prove difficult to identify independent risk separate from the infection.

Intensive Care Unit

Recent work has evaluated whether admission to or prolonged stay in the ICU is a risk factor for HA-VTE. One study demonstrated ICU admission confers independent VTE risk in all pediatric patients (27). Two studies in pediatric trauma have demonstrated independent VTE risk with ICU admission and ICU stay ≥4 days (34, 35). It is likely that ICU admission or prolonged stay is a proxy for illness severity and need for additional interventions, e.g., CVCs, mechanical ventilation that directly contributes to increased VTE risk.

Length of Stay

While recent data have highlighted extended LOS *following* HA-VTE, the mechanism by which prolonged hospitalization increases risk is less clear (2). Compounding the challenge are differences in analysis. LOS is a continuous variable but has been analyzed as both a continuous and a dichotomous variable. In two independent retrospective, case–control studies, Branchford et al. and Sharathkumar et al. utilized greater than 5 and 7 days, respectively, as cutoff values for increased VTE risk based on the distribution around the day of hospitalization on which VTE occurred (27, 36). Branchford et al. reported the odds of HA-VTE increasing by 3% for each additional day beyond 5 days. Pediatric trauma-specific literature has demonstrated daily increases in HA-VTE risk of 2 and 3% for those admitted with traumatic brain injury and general trauma, respectively (37, 38). Future research detailing increases in daily risk in the context of concomitant risk factors and whether risk can also decrease with elimination of other risk factors is lacking but would prove beneficial in understanding how LOS impacts VTE risk.

Mechanical Ventilation

Mechanical ventilation is emerging as a risk factor, but the magnitude of independent risk is unclear. Similar to ICU admission, mechanical ventilation may be a proxy for a severely ill child. In both trauma and critical care pediatric populations, mechanical ventilation has been identified as an independent VTE risk factor (36–38). One study observed an increased risk with ≥4 days of mechanical ventilation (35). Determining how independent risk for VTE increases with each additional day of mechanical ventilation, outside of the trauma setting requires investigation.

Obesity

Being overweight and obese in pediatrics is defined as body mass indices of 85th–94th and ≥95th percentiles, respectively (39). Obesity increases VTE risk through a chronic low-grade inflammatory state, platelet activation, and endothelial dysfunction (40). VTE risk due to obesity has been well-characterized in adults (41). Minimal pediatric-specific data exist. A retrospective, case–control study of 48 children with VTE identified increased risk in obese children but not overweight children. This study was confounded by frequent co-occurrence of known risk factors in obese children and a small sample size (42).

Oral Contraceptive Pills

Venous thromboembolism risk with combined oral contraceptive pills (COCPs) has been studied extensively. Estrogen has a multitude of mechanisms that increase thrombotic risk including increases in pro-coagulant proteins, decreases in counter-regulatory proteins including protein S and antithrombin, and inducing protein C resistance (43). While differences exist between route of delivery, type of progesterone, and the doses of estrogen and progesterone, the highest level of risk is thought to occur in the first 3 months of use and gradually plateaus after 12 months of use (44). The overall relative risk is threefold to fivefold higher than non-users of COCPs. Risk increases significantly with concomitant inherited thrombophilia (45). Studies examining VTE risk of progesterone-only contraception are conflicting. Some studies have shown increased risk, particularly with depot medroxyprogesterone and high-dose oral progesterone, whereas other studies have observed no increase in baseline risk, primarily with low-dose oral progesterone and progesterone-only intra-uterine implantable devices (44).

Surgery

Similar to infection, analyzing surgery is problematic given broad use of the term. Surgery is often reported as a risk factor without defining risk related to a specific procedure or its duration (15, 46). Procedures may be divided into major or minor, but these are neither consistently nor uniformly defined. For example, Van Arendonk et al. defined major surgery as involving the nervous, respiratory, cardiovascular, digestive, urinary, or musculoskeletal systems or spleen (38). Furthermore, not all studies defined the time interval between surgery and VTE. Previous work has defined VTE risk as 7 and 15 days prior to VTE diagnosis (46, 47). The duration of surgery has yet to be explored in pediatrics, but adult data have shown increasing VTE risk with increasing surgery duration (48).

RISK-ASSESSMENT MODELS

Several risk-assessment models have been published for pediatric HA-VTE (**Table 1**) (23, 36, 49–52). Branchford et al. showed independent risk with mechanical ventilation, systemic infection, and hospital stay ≥5 days, and that these three factors co-occurring yielded a posttest probability of 3.1% for HA-VTE (36). Sharathkumar et al. derived six independent risk factors and assigned points from beta coefficients in the logistic regression model: immobilization (3), LOS ≥ 7 days (2), OCPs (2), CVC (1), bacteremia (1), and direct ICU admission (0.5). A cumulative score of ≥3 yielded a positive predictive value of 2.45% for HA-VTE at a prevalence of 0.71% (27).

Two separate risk-assessment models, one for critically ill children and another for non-critically ill children, were created from a single institution during the same time period by retrospective, case–control study designs (23, 49). In non-critically ill children, scores of 8, 7, and ≤6 correlated to risk of HA-VTE of 12.5, 1.1, and 0.1%, respectively (49). In critically ill children, scores of 15, 7–14, and ≤6 correlated to risk of HA-VTE of 8.8, 1.3, and 0.03%, respectively (23).

TABLE 1 | Pediatric venous thromboembolism risk-assessment models.

	Branchford et al. (36)	Sharathkumar et al. (27)	Arlikar et al. (23)	Atchison et al. (49)	Reiter et al. (52)[a]	Kerlin et al. (50, 53)
Pediatric population	All	All	ICU	Non-ICU	ICU	All
Study design for score derivation	Retrospective case–control (1:2)	Retrospective case–control (1:2)	Retrospective case–control (1:3)	Retrospective case–control (1:7)	Literature review	Retrospective cohort
N	78:160	173:346	57:171	50:350		389
Validation method		Retrospective case–control (1:1)			Prospective, observational cohort study	Retrospective cohort
N		100:100			742	149
Risk factors comprising score	MV Infection LOS ≥ 5 days	Immobilization LOS ≥ 7 days OCP CVC Bacteremia Direct ICU admit	CVC LOS ≥ 4 days Infection	CVC Infection LOS ≥ 4 days	CVC Immobility >72 h Infection Orthopedic surgery Major trauma (ISS > 15) Malignancy OCP Burns >30% BSA Thrombophilia Age <1 or >14 years Obesity Hypercoagulable state	Male gender Asymmetric extremity CVC Active cancer Alternative diagnosis[b]

ICU, intensive care unit; MV, mechanical ventilation; LOS, length of stay; OCP, oral contraceptive pill; CVC, central venous catheters; ISS, injury severity score; BSA, body surface area.

[a]*Included venous and arterial thromboembolism in their study.*

[b]*Presence of this factor results in point reduction from score.*

Kerlin et al. derived an equation that uses 0 or 1 for absence or presence of certain factors (53):

$$\text{VET probability} = \{e^{[1.086\,(\text{male}) + 0.595\,(\text{asymmetric extremity}) + 0.643\,(\text{CVC}) + 0.549\,(\text{active cancer}) - 1.11\,(\text{alternative diagnosis}) - 2.03]}\} / \{1 + e^{[1.086\,(\text{male}) + 0.595\,(\text{asymmetric extremity}) + 0.643\,(\text{CVC}) + 0.549\,(\text{active cancer}) - 1.11\,(\text{alternative diagnosis}) - 2.03]}\}$$

Reiter et al. created an ICU-specific risk-assessment model (excluded cardiac ICU) for "pre-hospital" and "in-hospital" thromboses but included both venous and arterial events (52). They derived 12 risk factors from existing literature and weighted them equally with 1 point. They found for every 1 point increase in total score, the risk of a symptomatic thrombosis increased by 1.57-fold (95% confidence interval 0.132–5.49) to 2.12-fold (95% confidence interval 0.175–18.34) for "pre-hospital" and "in-hospital" thrombi, respectively ($p < 0.05$) (52).

The model by Prentiss describes levels of risk, Risk Score 1–3, but neither details which risk factors comprise the scoring system nor their individual point values (51). Additional models have been derived for children with acute lymphoblastic leukemia (54), pediatric oncology patients with a CVC-related VTE (55), and pediatric trauma (56).

To date, a multi-institutional risk-assessment model has been lacking in the literature, but current research is underway to address this gap (57). The Children's Hospital-Acquired Thrombosis (CHAT) Registry is a multi-institution registry with three planned phases of research. The first phase is a retrospectively derived risk-assessment model based on logistic regression. There are seven institutions contributing cases and controls (1:2), and as of January 1, 2017, there are 647 unique subjects with VTE in the registry (enrollment ongoing). Once the risk-assessment model is developed, it will be prospectively validated it in a separate multi-institutional study, i.e., phase 2. If validated, a randomized controlled trial investigating the utility of the CHAT risk-assessment model will be designed and conducted as the third phase.

MORBIDITY

Acute VTE sequelae depend on location and severity. Pulmonary thromboses may lead to pulmonary hypertension or cardiovascular instability. Thrombosis of the superior vena cava (SVC) or thoracic vessels may result in SVC syndrome. Extremity DVTs induce pain and swelling. VTE in patients with renal disease has been associated with 2-fold increase in hospital admissions and 10-fold increase in LOS (53). Neonates have increased risk of chronic renal insufficiency following renal vein thrombosis.

Risk of VTE recurrence has been variably reported but is estimated around 10% in children and 3% in neonates (9, 18). Comorbidities such as cardiovascular disease, malignancy, and neurovascular disorders have been associated with increased likelihood of recurrence. Patients with identified thrombophilia variants, e.g., prothrombin gene mutation and antithrombin deficiency, may also be at increased risk of recurrent VTE. PTS, chronic venous insufficiency associated extremity pain, edema,

and stasis dermatitis, appear less frequent and severe in children (12.4%) compared to adults (30%); however, this likely represents underreporting as outcomes studies are limited and most have relatively short durations of follow-up (58). PTS occurs most commonly in the lower extremities. Recently, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommended use of a pediatric modification of the Villalta score for adult PTS to standardize reporting in children (11).

MORTALITY

Venous thromboembolism in children is associated with increased mortality. VTE mortality rates of 11.4 per 1,000 child-years have been reported, greater than age-specific mortality estimated at 6.4 per 1,000 child-years in a population-based study conducted in Canada (5). This finding is consistent with data from several registries that report all-cause mortality in those with VTE of 9–17%. In one study, over 20% of deaths were noted to occur within 30 days of VTE diagnosis (8). The highest mortality rate is in the youngest patients. Fortunately, mortality rates directly attributed to VTE are low, 1.5–2.2%. Risk of fatality associated with pulmonary embolism is less in pediatrics compared to adults (59).

CONCLUSION

Pediatric VTE is increasing in incidence. Key contrasting points between adults and children are that pediatric VTE is more likely to be diagnosed in a hospital and have recognizable antecedent provocation. As incidence increases, associated morbidities, mortality, and health-care costs do likewise. Clearer understanding of pediatric-specific risk factors and validated risk-assessment models are needed to reduce preventable harm and investigate the efficacy of targeted prophylaxis interventions. A multitude of risk factors have been identified for pediatric VTE, but many need further elucidation. Similarly, risk-assessment models to date provide an initial approach but ultimately lack prospective validation and correlation to outcomes. The multi-institution CHAT registry is poised to overcome these limitations and provide details regarding the magnitude of risk attributable to patient, disease, and interventional factors. Initial results are anticipated in 2017. If successful, the CHAT Registry may serve as the foundation of a risk-stratified, randomized controlled trial to evaluate thromboprophylaxis measures in pediatrics.

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The Role of Inflammation in Venous Thromboembolism

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Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT), and pulmonary embolism (PE), is becoming increasingly recognized as a cause of morbidity and mortality in pediatrics, particularly among hospitalized children. Furthermore, evidence is accumulating that suggests the inflammatory response may be a cause, as well as consequence, of VTE, but current anticoagulation treatment regimens are not designed to inhibit inflammation. In fact, many established clinical VTE risk factors such as surgery, obesity, cystic fibrosis, sepsis, systemic infection, cancer, inflammatory bowel disease, and lupus likely modulate thrombosis through inflammatory mediators. Unlike other traumatic mechanisms of thrombosis involving vascular transection and subsequent exposure of subendothelial collagen and other procoagulant extracellular matrix materials, inflammation of the vessel wall may initiate thrombosis on an intact vein. Activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles can trigger the coagulation system through the induction of tissue factor (TF). Identification of biomarkers to evaluate VTE risk could be of great use to the clinician caring for a patient with inflammatory disease to guide decisions regarding the risk:benefit ratio of various types of potential thromboprophylaxis strategies, or suggest a role for anti-inflammatory therapy. Unfortunately, no such validated inflammatory scoring system yet exists, though research in this area is ongoing. Elevation of C-reactive protein, IL-6, IL-8, and TNF-alpha during a response to systemic inflammation have been associated with increased VTE risk. Consequent platelet activation enhances the prothrombotic state, leading to VTE development, particularly in patients with other risk factors, most notably central venous catheters.

Keywords: pediatrics, venous thromboembolism, thrombosis, inflammation, cytokines, platelets, risk factors

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Evidence is accumulating that the factors influencing VTE formation are not restricted to the coagulation system alone, but rather that the immune system is also closely involved with formation and resolution of thrombosis. It is important to consider the contributions of inflammation to VTE development in general, but also as it pertains to certain specific disease categories more commonly associated with development of hospital-acquired VTE (HA-VTE) in some patients. Surgery, (1–3) obesity, (4) cystic fibrosis, (5–7) sepsis, (8–10) systemic infection, (11, 12) cancer, (13–15) inflammatory bowel disease, (16–18), and lupus (19–22) are clinical VTE risk factors that may modulate thrombosis through inflammatory mediators. Understanding the role of inflammation in these particular clinical situations may not only help determine the optimal management but may also aid in the development of future preventative strategies, since current anticoagulation treatment regimens are not designed to inhibit inflammation (23).

Recently, inflammation has been accepted as a common pathway through which various risk factors trigger VTE formation. A feasible mechanism is that inflammation of the vessel wall initiates thrombus formation in an intact vein and that inflammation and coagulation systems are coupled by a common activation pathway. The first event in thrombus formation is probably activation of endothelial cells, platelets, and leukocytes, with initiation of inflammation and formation of microparticles that trigger the coagulation system through the induction of TF. Therefore, the key event in the initiation of VTE formation is most likely vein wall inflammation, but the contribution of specific immune modulators has not yet been elucidated. Recently, it was demonstrated that probable association between VTE and several other markers of inflammation such as C-reactive protein (CRP), IL-6, IL-8, and tumor necrosis factor-alpha exists (24–28). These pro-inflammatory cytokines play an important role in VTE by promoting a pro-coagulant state primarily by inducing the expression of tissue factor. Several immune system components (cytokines, chemokines, and various leukocyte subtypes) are involved in the underlying inflammatory process of VTE, as is very well-described in a recent review from Saghazadeh et al. (23). Additionally, it has been recently described that inflammatory mediators such as polyphosphates, bradykinin, and others may directly activate the contact system (the polyphosphate—Factor XII association is particularly notable) and initiate the extrinsic coagulation pathway (29–31).

The identification and elucidation of inflammatory markers relevant to VTE could provide targets for future therapy. That inflammation is the basic etiopathogenic process of VTE is also supported by the relation of some risk factors to both arterial and venous thrombosis: age, increased BMI, atherosclerotic disease, hypercholesterolemia, hypertension, antiphospholipid antibodies, and hyperhomocysteinemia (28).

INTERACTION BETWEEN COAGULATION AND INFLAMMATION

For over a century, thrombosis formation has been attributed to three main groups of factors including alterations in blood flow, endothelial injury, and hypercoagulable state, collectively known as Virchow's Triad (32). A prime example is the frequent association of central venous catheter (CVC) with VTE. Blood flow is altered by the obstacle in the vein, creating turbulent flow in some areas, while promoting stasis in others, depending on local vascular architecture. Additionally, the endothelium is damaged at the catheter insertion site, and the body actively attempts to repair that site with primary and secondary hemostatic efforts. Finally, there is a high likelihood that the underlying disease process that necessitated the need for the CVC in the first place (volume resuscitation in trauma or distributive shock, chemotherapy administration for active cancer, long-term antibiotics for severe infection, etc.) increases the risk for thrombosis. There is also likely a reciprocal relationship between CVC infections leading to increasing risk for line thrombosis and infected clots within a line likely to adversely affect its function. Over the last decade, a growing body of evidence suggests a role for consideration of inflammation as a major contributor to the pathophysiology of VTE, (33) likely by enhancing the hypercoagulable state and increasing endothelial damage. Activation of endothelial cells, platelets, and leukocytes, with subsequent initiation of inflammation and microparticle formation, triggers the coagulation system through induction of TF, primarily that borne by microparticles, which may contribute to the hypercoagulable state in the Triad (28, 34, 35). Both formation and resolution of thrombosis have been associated with a series of inflammatory cascades (36, 37). Moderate to severe degrees of inflammation (inflammatory infiltrates throughout the thrombi, mostly composed of lymphocytes, with some mixing of other components including plasma cells, neutrophils, and eosinophils) (38) were found in approximately 15% of thrombus specimens from pulmonary thromboendarterectomy (23) and immunity/inflammatory genes constitute nearly 10% of those genes whose expressions are substantially altered under the influence of VTE (38, 39). A reciprocal relationship exists in which patients with VTE have an increased risk of myocardial infarction and stroke, and vice versa, while proven cardiovascular risk factors such as obesity, tobacco use, diabetes, stress, and diet increase the risk of both atherothrombotic events and VTE, likely due to the common pathophysiological mechanism of promoting cardiovascular inflammation (40).

Evidence of specific pathophysiologic links between the coagulation system and innate immunity continues to mount. Polyphosphate (polyP) is present in human platelet dense granules and is released upon platelet activation, assisting with coagulation by increasing activation of factor V, decreasing tissue factor pathway inhibitor (TFPI) activity, and delaying clot lysis by activating thrombin-activatable fibrinolysis inhibitor (TAFI) (41–44). PolyP is also a potent pro-inflammatory signal when released from mast cells during a hypersensitivity reaction, for example (42).

Additionally, histones have been shown to be increased in sepsis and other inflammatory conditions along with nucleosomes (DNA + histones), and are toxic to the endothelium. Activated protein C inactivates histones, protecting the endothelium in the process (45). Extracellular DNA fibers extruded from neutrophils (Neutrophil Extracellular Traps, NETs) are produced in response to infection to allow neutrophils to trap and destroy invading microorganisms. Fibrin formation and deposition has been shown to be stimulated by NETs, and fibrin formation is also important in trapping organisms and controlling infection (46). NETs also cause platelet adhesion and have been shown to be linked to deep vein thrombosis in experimental models (47). Moreover, platelets have been shown to stimulate NET production (46). There is also evidence that some bacteria interact with platelets, either directly or through antibody-mediated mechanisms, leading to platelet activation or contributing to thrombus development. Other interactions have been identified which are beyond the scope of this brief review and have been described excellently elsewhere (45, 48–50).

Inflammation can be both a cause and a consequence of VTE, but current anti-coagulation treatment regimens are not

specifically designed to inhibit inflammation (though it is known that heparins have some anti-inflammatory effects). Selective pharmacologic targeting of immune/inflammatory mediators in VTE may result in more effective therapeutic or prophylactic strategies (23). It is important to note, however, that the role of anti-inflammatory therapies in VTE prevention efforts is still not well-established. One study demonstrated a 2-fold or more increased risk of VTE with the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2-selective (COX-2) inhibitors (51). These results were reflected in a recent systematic review and meta-analysis in which the pooled risk ratio among NSAID users was 1.8-fold for VTE (52). Adequate VTE mechanism data in this setting are not yet available, however, to determine whether the anti-inflammatory medication itself drives the VTE formation or whether inflammation drives the usage in patients who are being treated with anti-inflammatory drugs to manage their underlying medical condition. The same question may be considered in users of steroids, though it has been shown more specifically that glucocorticoids increase levels of clotting factors and fibrinogen, which may explain the elevated VTE risk (especially pulmonary embolism) demonstrated in a recent Danish study of glucocorticoid users that followed an associated temporal pattern, persisted after adjustment for underlying disease severity, and existed even in non-inflammatory conditions (53). A similar effect with 1.5-fold increased VTE risk was seen in subjects treated with glucocorticoids for at least 30 days prior to surgery (54).

Particular disease subgroup-specific relationships have been studied, as seen below and in **Table 1**.

SURGERY AND TRAUMA

Surgery and trauma are linked in terms of HA-VTE risk due to the tissue injury they have in common. The role of inflammation in driving HA-VTE risk in these clinical situations is primarily related to the process through which transected vessels and tissue undergo physiologic repair. The innate immune system is activated following tissue injury, platelets degranulate locally after recruitment from the circulation, and tissue macrophages and mast cells are activated with a combined effect of leukocyte chemoattraction (55). Neutrophils infiltrate the wound, followed by additional circulating monocytes that differentiate into mature tissue macrophages, (56) and later by additional infiltration of mast cells from adjacent tissue (57), and finally by T-lymphocytes (58). The collective result of these cellular activation processes is increased release of IL-1, IL-6, IL-12, and TNFα (59, 60). IL-6 has been demonstrated to play a critical role in inflammation-related thrombosis (61) increased concentrations of IL-6, along with TNFα and IL-8 are potent risk predictors for VTE, even after adjustment for covariates, including CRP (62). Additional neutrophil presence (following chemoattractant release from platelets and mast cells) and subsequent NET formation have been linked to venous thrombosis (47, 63). The interaction between endothelial E-selectin, leukocyte L-selectin, and platelet P-selectin also plays an important role in platelet-leukocyte aggregation and adherence to vessel walls at sites of surgical or traumatic injury. P-selectin inhibition has been shown to decrease venous thrombosis in murine (64) thrombosis models and enhance thrombus resolution in rat models (65). Similarly, E-selectin inhibition with a small molecule inhibitor has been shown to decrease inflammation (vein wall monocyte extravasation) and acute venous thrombosis in a surgical model of murine thrombosis induction (66) and is now being studied in early clinical trials in humans.

INFLAMMATORY BOWEL DISEASE

Among VTE-related hospitalizations, the presence of IBD was associated with a 2.5-fold increased risk of mortality in one population-based study (18). No studies have specifically evaluated the potential benefit of VTE prophylaxis in hospitalized or ambulatory IBD patients, but studies to date do not support an increased bleeding risk with moderate doses of anticoagulant medications in IBD patients with active disease (18). Recent large studies have quantified this risk showing that IBD patients run a 1.5 to 3.6 higher risk of developing VTE than healthy controls (16, 17). IBD has been demonstrated to represent an independent risk factor for the recurrence of VTE (17).

IBD has been previously associated with increased levels of TNFα (67) with upregulation of TNFα mRNA in colonic tissue in patients with Crohn's Disease (68) and Ulcerative Colitis (69) and many current therapeutic regimens involve a focus on blocking signaling through this molecule. Giannotta et al. (16) have recently reviewed the specific effects of TNFα on activation of intrinsic coagulation pathway by inducing tissue factor expression on leukocyte surfaces, down-regulation of natural anticoagulants (protein C and heparin-antithrombin pathways) in addition to thrombomodulin and the endothelial protein C receptor, increasing platelet production and enhancing thrombin formation in conjunction with IL-6, and triggering (in conjunction with IBD-associated elevation in homocysteine) expression of vascular cell adhesion protein-1 and monocyte chemoattractant protein 1 on endothelial surfaces leading to enhanced capacity to recruit T cells and monocytes.

OBESITY

Obesity is a known risk factor for arterial and venous thrombosis. Studies have shown that obesity conveys an odds ratio of 1.7–2.2 for VTE, similar to that of other known VTE risk factors (70). A recent cohort of 268 adults with incident VTE events over 4.6 years from the Reasons for Geographic And Racial Differences (REGARDS) cohort demonstrated that higher CRP levels and lower serum albumin levels were associated with increased VTE risk and statistically mediated part of the association of body mass index (BMI) with VTE, suggesting that inflammation may be a potential mechanism underlying the relationship between obesity and VTE risk. White blood cell (WBC) count and platelet

TABLE 1 | Inflammatory considerations in specific clinical situations.

Clinical subgroup	Inflammatory considerations
Surgery	The healing process is, at baseline, inflammatory since this is the mechanism by which tissues are re-approximated and cellular debris is cleared. Surgery may also be in response to an inflammatory stimulus (e.g., cancer, abscess, trauma). SCD usage may be helpful in surgeries extending over a certain time duration because of their mechanism of replacing the venous return assistance usually provided by the body's lower extremity muscle contractions while walking.
Inflammatory bowel disease	Various reports of odds ratio between 1.5 and 3.5 for increased VTE risk in patients with IBD. Primary risk factors in this subgroup include disease severity, colonic localization, and recent surgery. Risk decreases with treatment of underlying condition.
Obesity	Obesity confers an odds ratio between 1.7 and 2.2 for VTE, likely acting through higher CRP levels found in subjects with higher BMI, in addition to potential for decreased physical activity.
Cystic fibrosis	Multifactorial increased VTE risk: frequent hospitalizations, systemic or severe local infections (especially with specifically thrombogenic strains such as *B. cepacia*), elevated acute phase reactants, CVC presence, activated platelets. Risk decreases with appropriate management of underlying condition.
Sepsis/systemic infection	Specific risk from acute phase reactant release (tissue factor, VWF, procoagulant microparticles), inhibition of fibrinolysis, NET formation, etc. Risk is increased in both systemic and severe local infections.
Systemic lupus erythematosus	Particularly challenging due to existence of both chronic and acute inflammatory-driven risk states and auto-immune component (APLA, innate immune dysregulation, etc.). Risk decreases with treatment of underlying condition.

count were not determined to have any relationship. Adipocytes secrete inflammatory cytokines leading to chronic, low-grade inflammation resulting from recruitment of macrophages to adipose tissues that progressively accumulate as fat mass increases, and drive a progression of anti-inflammatory M2 macrophages to proinflammatory M1 macrophages, leading to increased secretion of proinflammatory cytokines including TNFα, IL-6, and IL-1β, as well as impaired fibrinolysis due to marked increase in plasminogen activator inhibitor-1 expression (70). These proinflammatory cytokines, as well as adipokines such as leptin, stimulate vascular endothelium, platelets, and other circulating vascular cells, leading to upregulation of procoagulant factors including tissue factor and cellular adhesion molecules, downregulation of anticoagulant regulatory proteins, increased thrombin generation, and enhanced platelet activation (71). Finally, aberrant microRNA expression patterns likely contribute to thrombosis in obesity through decreased endothelial nitric oxide bioavailability, unregulated expression of endothelial adhesion molecules, and enhanced platelet activation and degranulation as reviewed by Blokhin and Lentz (72).

CYSTIC FIBROSIS (CF)

CF is a multi-system inflammatory disease, complicated by excessive production of thick mucus secretions that lead to pulmonary infectious exacerbations resulting in hospitalization for IV antibiotics, frequently through a CVC. These patients have increased risk of thrombosis due to CVCs, as well as acquired thrombophilia secondary to inflammation [including both the elevation of pro-coagulant acute phase reactant proteins such as fibrinogen, factor VIII, and/or von Willebrand factor (VWF), as well as the suppression of protein S by inflammation-related C4B binding protein], or natural anticoagulant protein deficiencies due to vitamin K deficiency and/or liver dysfunction (6). Also, the incidence of antiphospholipid antibodies that may be associated with increased thrombotic risk ranges from about 5–10% in patients with CF, which is elevated compared to that reported in healthy children (1–3%) (73, 74). While platelets are generally thought to play a more significant role in the pathogenesis of arterial thrombosis (coronary heart disease and stroke), it has been postulated that activated platelets may contribute to pulmonary inflammation and tissue destruction in CF, specifically (75). Certain specific pulmonary infections, such as *Burkholderia cepacia,* may also increase VTE risk in CF patients (76).

VTE in children with cystic fibrosis was recently studied at a single center and the incidence rate was found to be 53 VTE cases per 10,000 children with CF. Several inflammatory-specific risk factors for VTE were reported, including sinus disease, positive respiratory cultures, and elevated inflammatory markers such as erythrocyte sedimentation rate and CRP (7). A recent retrospective study of 116 adults with CF hospitalized for pulmonary exacerbations using a CVC demonstrated a 2.5% incidence of catheter-related VTE (77). Elevated CRP was associated with the thrombosis group but did not reach statistical significance ($p = 0.51$) and the time to VTE development was shorter for peripherally-inserted central catheter (PICC) lines compared to Port-a-Cath, though the only two recurrent events occurred in subjects with Port-a-Caths (77). A prospective study of 90 adult and pediatric CF patients, on the other hand, demonstrated a CVC-related VTE frequency of 6.6% (combination of symptomatic clots and those detected by screening ultrasound) (5). This study did not identify biomarkers (CRP, D-dimer, fibrinogen) for inflammatory/hypercoagulable screening at the time of catheter insertion, but did emphasize the contribution of VTE history and raises the issue of prospective Doppler ultrasound for consideration in identifying asymptomatic CVC-VTEs, though the role of anticoagulant therapy in the management of these patients remains controversial. The utility of pharmacologic

prophylaxis for the prevention of CVC-associated thrombosis, particularly in high risk CF individuals, deserves further study (6).

SEPSIS AND SYSTEMIC INFECTION

Bacterial sepsis is a classic example of inflammation-triggered coagulation induced by endothelial injury and tissue factor expression following an acute systemic inflammatory response, (78) leading to activation and consumption of coagulation factors and platelets, along with impaired fibrinolysis, disruption of endothelial barrier, and loss of physiologic antithrombotic factors such as thrombomodulin (79). Sepsis denotes progressively more severe host defense reactions to invading organisms with endothelial dysfunction and elevation of inflammatory markers triggering the activation of coagulation with concurrent down-regulation of anticoagulant systems and fibrinolysis (disseminated intravascular coagulation, DIC) which, in turn, contributes to increased inflammation. There is significant interplay between inflammation and coagulation in sepsis, highlighted by the procoagulant properties of the endothelium such as expression of tissue factor (TF) and VWF, activating interactions with platelets, release of procoagulant microparticles, and downregulation of TF pathway inhibitor (TFPI) and the protein C/S anticoagulant system, inhibiting fibrinolysis. The coagulation response serves to isolate the invasive organism, but some bacteria have adapted to this and can use the coagulation response to hide from immune attack (12, 46, 80).

As mentioned above regarding *B. cepacia* specifically imparting elevated VTE risk in CF patients, certain clinical variables and bacterial virulence factors are associated with VTE in *Staphylococcus aureus* bacteremia (Methicillin-resistance, CRP >20 mg/dL, and hemoglobin nadir </= 9 g/dL, though it may not always be clear whether anemia was an additional factor in the development of thrombus or is a marker of more severe disease) (11). These findings were comparable to those from another study of 70 children with osteomyelitis where in an elevated CRP was associated with increased VTE risk (81). Furthermore, a study of over 10,000 subjects in the Atherosclerosis Risk in Communities (ARIC) study, CRP above the 90th percentile was associated with a 76% increase in risk of VTE versus lower percentiles (24). A recent study of 39,831 patients who underwent colorectal surgery demonstrated a 2.4% incidence of VTE, associated with urinary tract infections, pneumonia, organ space surgical site infection, or deep surgical site infection (3).

SYSTEMIC LUPUS ERYTHEMATOSUS

In general, inflammatory rheumatologic diseases (lupus, Sjogren's syndrome, inflammatory myositis, and systemic sclerosis) are associated with high VTE rates—more than three times higher than in the general population (22). In particular, patients with systemic lupus erythematosus (SLE) are at significantly increased risk for premature atherosclerosis and thrombosis not only due to direct effects of chronic systemic inflammation but also to the additional risk imparted by antiphospholipid antibodies (21). This acquired, multi-organ, autoimmune disease itself is an independent risk factor for both arterial and venous thrombotic events, particularly in those with the antiphospholipid syndrome. Myriad factors influence atherosclerosis and cardiovascular disease in SLE patients, including those related to the disease itself (INF-alpha, TNF-alpha, MCP-1, cystatin C, kidney disease, overexpression of ICAM/VCAM/VEGF/VWF, NETs, elevations of interleukins 6/12/17/18, and other acute phase reactants) and to the medications used to treat it (corticosteroids, antimalarials, mycophenolate mofetil, HMG-CoA reductase inhibitors, and non-steroidal anti-inflammatories) (20). Individuals with SLE have been shown to have decreased DNase1 activity in their serum, which decreases NET degradation, and may contribute to thrombus formation (47). Activation of the innate immune system as evidenced by the elevation of TNF-alpha and the interleukins described above increases the risk of VTE even after adjustment for CRP (62). Polymorphisms in genes encoding factor VIII, Interleukin-1β, and interleukin-10 have been shown to modulate the risk of idiopathic VTE (82).

The lupus nephritis and autoimmune thrombocytopenia found in some of these patients also complicate the anticoagulant strategies and their standardization, but consistent APLA screening, renal evaluation/management, and use of hydroxycholorquine may decrease thrombotic risk or at least disease-related morbidity/mortality (19).

CONCLUSION

Clinical observations and mounting laboratory evidence support a complex interplay between inflammation, innate immunity, and the coagulation system. As more is understood about these interactions, novel preventive and treatment modalities for thrombosis will likely become available.

AUTHOR CONTRIBUTIONS

BB and SC contributed equally to the preliminary literature review, as well as the writing and revision of the manuscript.

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Inherited Thrombophilia in Pediatric Venous Thromboembolic Disease: Why and Who to Test

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Venous thromboembolic disease in childhood is a multifactorial disease. Risk factors include acquired clinical risk factors such as a central venous catheter and underlying disease and inherited thrombophilia. Inherited thrombophilia is defined as a genetically determined tendency to develop venous thromboembolism. In contrast to adults, acquired clinical risk factors play a larger role than inherited thrombophilia in the development of thrombotic disease in children. The contributing role of inherited thrombophilia is not clear in many pediatric thrombotic events, especially catheter-related thrombosis. Furthermore, identification of inherited thrombophilia will not often influence acute management of the thrombotic event as well as the duration of anticoagulation. In some patients, however, detection of inherited thrombophilia may lead to identification of other family members who can be counseled for their thrombotic risk. This article discusses the potential arguments for testing of inherited thrombophilia, including factor V Leiden mutation, prothrombin mutation, and deficiencies of antithrombin, protein C, or protein S and suggests some patient groups in childhood, which may be tested.

Keywords: thrombophilia, venous thromboembolism, pediatric, risk factor, counseling

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INTRODUCTION

Venous thromboembolism (VTE) is increasingly recognized in children. In the 1990s, the annual incidence was estimated to be 0.07–0.14 per 10,000 children (1, 2). Since then, studies showed more and more children developing thromboembolic complications as a result of improved diagnosis, increased survival of children with severe underlying diseases, and increased use of invasive procedures and instruments such as central venous catheters. From 2001 to 2007, diagnosis of VTE increased from 34 to 58 cases per 10,000 hospital admissions in the United States (3). This increase was observed in all age categories. Neonates and adolescents have the greatest risk for VTE (4). It is a serious disease, which leads to mortality and morbidity. The mortality rate is about 2%. Morbidity includes lack of thrombus resolution in 50% of the patients and the development of post thrombotic syndrome in about 30% of the patients (5).

In contrast to adults, most of the venous thrombi in children are associated with clinical risk factors. In neonates, more than 90% of the thrombi are catheter related. In older children, catheters are important risk factors as well, as about 50% of VTE are associated with central venous catheters (4).

Abbreviations: VTE, venous thromboembolism; FVL, factor V Leiden mutation; FIIm, prothrombin mutation; CI, confidence interval.

In addition, other clinical risk factors contribute to the thrombotic risk, including cardiac disease, malignancy, surgery, immobility, and medications such as asparaginase and estrogen-containing contraceptives. These clinical risk factors may trigger VTE in thrombophilia carrier patients. It is still a matter of debate whether it is useful to test thrombophilia in children with a first venous thrombotic event. This article will discuss the potential arguments for testing of inherited thrombophilia, including factor V Leiden mutation (FVL), prothrombin mutation (FIIm), and deficiencies of antithrombin, protein C, or protein S and suggests some pediatric patient groups, which may be candidates for testing.

INHERITED THROMBOPHILIA

Inherited thrombophilia is defined as an inherited coagulation disorder associated with an increased risk for thrombosis. The most frequent inherited thrombophilic defects include deficiencies of antithrombin, protein C, protein S, FVL, and FIIm.

Antithrombin deficiency was the first identified genetic risk factor for VTE. In 1965, Egeberg reported a family with increased risk for venous thrombosis due to antithrombin deficiency (6). He was the first who used the term thrombophilia. Antithrombin deficiency appears to be very scarce with a prevalence of about 0.02% in the general population (7).

Antithrombin inhibits several enzymes of the coagulation system including factor IIa, IXa, Xa, and XIIa. Type I deficiency is associated with low antithrombin antigen and activity levels. Type II deficiency is characterized by decreased functional activity. Homozygous antithrombin deficiency type I patients have not been described, assuming complete antithrombin deficiency is not compatible with life.

Protein C and protein S act together to inactivate factor Va and factor VIIIa. Protein C deficiency has been recognized since 1981 (8). Since then, more than 160 mutations have been identified. The prevalence of protein C deficiency is estimated to be about 2% (7). Two types of protein C deficiency have been described. Type 1 deficiency is associated with decreased antigenic levels as well as functional activities of protein C. In type II deficiency, the activity levels of protein C are more decreased than the antigenic levels.

Protein S deficiency has first been described in 1984 (9). The prevalence is low and varies between 0.026 and 0.13% (7). Two forms of protein S are present in the plasma: about 60% is bound to complement regulator C4b-binding protein and the remaining 40% circulates as free protein S. Only free protein S can serve as a cofactor for activated protein C. There are three types of protein S deficiency. Types I and III are quantitative deficiencies. In type I, levels of both free and total protein S are low, whereas only free protein S levels are decreased in type III deficiency. Type II deficiency is a qualitative disorder with normal antigen and decreased activity levels of protein S.

Both protein C and S deficiency can present in heterozygous, homozygous, or compound heterozygous forms, although the last two forms are extremely rare. These patients present with neonatal purpura fulminans (10, 11). In infancy, diagnosis of homozygous protein C or S deficiency can be made by measuring the functional activity of protein C or S, which will be undetectable. Diagnosis of heterozygous protein C, S, or antithrombin deficiency, however, will be challenging as all anticoagulant protein levels are physiologically lower in healthy (preterm) neonates compared to adult levels as result of developmental hemostasis (12). Protein S and antithrombin levels reach adult levels over the first 6 months of life. Protein C levels may remain low until adolescence (13).

FVL is the most common inherited thrombophilic defect although its prevalence varies widely. Prevalences of heterozygous FVL range from 1 to 9% in European countries, whereas it is rarely found in African and Asian individuals (14). FVL is characterized by a substitution of glutamine by arginine on position 506 of the factor V protein at the activated protein C cleavage site. It causes resistance of factor Va to cleavage by activated protein C leading to an excess of factor Va and, consequently, a hypercoagulable state (15, 16).

FIIm is the second most common inherited thrombophilic defect. In Caucasians, the prevalence of this mutation is about 2% (17). It is characterized by a point mutation (nucleotide 20210 G to A) in the prothrombin gene, which is associated with increased levels of prothrombin, the precursor of thrombin (18). Increased levels of prothrombin increase the half-life of factor Va. As factor Va, bound in the prothrombin-factor Va complex, is resistant to activated protein C cleavage, increased levels of prothrombin increase the half-life of factor Va, leading to a hypercoagulable state.

WHY SHOULD WE TEST FOR INHERITED THROMBOPHILIA IN CHILDREN WITH A FIRST VENOUS THROMBOTIC EVENT?

In general, there are three possible arguments to test for thrombophilia in children with a first venous thrombotic event. First, if there is an association between inherited thrombophilia and the development of pediatric thrombosis, identification of a thrombophilic defect may help to learn why a young patient developed thrombosis, especially if the thrombotic event was unprovoked. Second, testing should be performed if a positive test result will change the patient's management, such as prolongation of anticoagulant prophylaxis of recurrent thrombotic events. Finally, testing pediatric patient with VTE may help to identify asymptomatic relatives who may avoid thrombotic risk factors and benefit from thromboprophylaxis in high-risk situations.

Association between Inherited Thrombophilia and Venous Thrombosis

Patients, parents, and their doctors would often like to have an explanation for the VTE event. Several case series, case-control studies, registries, and cohort studies have been published, which studied the impact of inherited thrombophilia on VTE in children. In 2008, Young et al included these studies in a meta-analysis, which showed that children with first-onset VTE were more likely to have inherited thrombophilia than controls (19). The odds ratios varied from 2.63 [95% confidence interval (CI), 1.61–4.29] for FIIm to 8.73 (95% CI, 3.12–24.42) for antithrombin

deficiency. These ORs resembled the relative risks found in adults with VTE (20). So, in general inherited thrombophilia contributes to the development of VTE in children. Testing for thrombophilia might reveal one of the causes of the thrombotic event in a pediatric patient. The identification of a thrombophilic defect, though, does not exclude other risk factors as shown in the meta-analysis. More than 70% of the patients had at least one clinical risk factor, illustrating that a thrombophilic defect alone is usually not enough to develop pediatric thrombosis.

The association between inherited thrombophilia and certain patient subgroups is less clear. An important limitation of the above-mentioned meta-analysis was that patient subgroups like provoked or unprovoked, neonatal VTE, and catheter-related VTE could not be analyzed separately due to small groups, and unclear definitions in the original studies. Nevertheless, other studies showed that the prevalence of inherited thrombophilia seems to be higher in adolescents with unprovoked thrombosis and in children with a positive family history for VTE and lower in children with cardiac disease or malignancy with catheter-related thrombosis (21–24). In neonates with catheter-related thrombosis, only a few small studies investigated the prevalence of thrombophilia defects, which were rarely found (25–27).

Thrombophilia and the Management of Thrombosis

A more important reason in favor of thrombophilia testing would be the need to adjust the management of thrombosis in case of a positive result. At the moment, the identification of an inherited thrombophilic defect does not alter the acute antithrombotic management in children (28). Whether the duration of anticoagulation will change after discovery of a thrombophilic defect is dependent on the risk of side effects of anticoagulation, such as major bleeding, the risk of recurrent VTE and the preference of the patient. In adults, the annual incidence of major bleeding from long-term anticoagulation is 1.5–2% (29, 30).

Generally, the cumulative recurrence-free survival in children is reported to be 92% after 1 year and 82% after 7 years of follow-up (24). Young et al. studied the association between inherited thrombophilia and recurrent VTE in children (19). Their meta-analysis showed a significant but mild association for all thrombophilic defects, except FVL. The ORs varied from 2.15 (95% CI, 1.12–4.10) for FIIm to 3.76 (95% CI, 1.76–8.04) for protein S deficiency. Children with two or more thrombophilic defects had the highest risk for recurrent VTE (OR 4.91; 95% CI, 3.12–7.74). The thrombotic recurrence risk in children with thrombophilia was slightly higher than that in adults (**Table 1**). This might be caused by lack of prophylactic anticoagulation in high-risk situations after the first thrombotic event. In children, it was not common practice to administer thromboprophylaxis in high-risk situations such as immobility, surgery, or trauma. In adults as well as in children, the mild increased recurrence risk in patients with inherited thrombophilia has not lead to adjustment of the duration of anticoagulant therapy.

Very recently, Limperger et al. studied the annual recurrence rate of pediatric patients after a first non-catheter-related VTE (31). In general, the estimated risk of VTE recurrence was 1.5% per year. In children with high-risk thrombophilia, the annual recurrence rates were 5.4% (95% CI, 2.6–10%) in children with antithrombin deficiency, but only 1.3% (95% CI, 0.3–3.8%) and 0.7% (95% CI, 0.08–2.4%) in protein C and protein S deficient patients, respectively. In patients with no thrombophilia, the annual recurrence rate was 0.9% (95% CI, 0.4–1.8%). Thus, based on these results, particularly antithrombin-deficient patients have an increased recurrence risk. These patients might be identified by testing and benefit from preventive strategies.

These preventive strategies may include indefinite anticoagulation with vitamin K antagonists or intermittent anticoagulation in high-risk situations. Both strategies have not been studied in children yet. As in the study of Limperger et al., 9 out of the 10 children with antithrombin deficiency had provoked recurrent VTE, the latter strategy with intermittent anticoagulation might be sufficient enough to prevent recurrent VTE with less risk of bleeding. One might argue, however, that every young patient should get intermittent prophylactic anticoagulation in high-risk situations after a first VTE, independent from the presence of inherited thrombophilia. Due to decreased bleeding risk, the new direct oral anticoagulants might appear to have a favorable benefit-to-risk ratio for prolonged anticoagulation in children with antithrombin deficiency in future.

Identification of Asymptomatic Relatives

It is suggested that inherited thrombophilia testing in pediatric patients with VTE allows the identification of asymptomatic family members with thrombophilia. The affected relatives will have the opportunity to avoid risk factors such as smoking and obesity to get informed about thrombotic risks of contraception and pregnancy and to use thromboprophylaxis in high-risk situations.

Holzhauer et al. investigated the general, annual incidence of VTE in first- and second-degree relatives of pediatric patients with VTE and inherited thrombophilia (32). The absolute risk of a first thrombotic event per year in asymptomatic relatives was not very high. It was higher in carriers of antithrombin, protein C or S deficiency (2.82%; 95% CI, 1.63–4.80%) than in carriers of FIIm or FVL (0.42%; 95% CI, 0.17–1.01% and 0.25%; 95% CI, 0.12–0.53%), respectively. In relatives without inherited thrombophilia, the absolute VTE risk per year was 0.10% (95% CI, 0.06–0.17%). As in adults, the inherited thrombophilic defects can, therefore, be divided in low-risk thrombophilia, including FVL and FIIm and high-risk thrombophilia, including deficiencies of antithrombin, protein C or S (32, 33). Remarkably, almost 65% of VTE in the first- and second-degree relatives of pediatric VTE patients with thrombophilia in the study of Holzhauer et al. was associated with clinical risk factors. Thus, discussion with asymptomatic relatives about avoidance of lifestyle risk factors such as obesity and smoking and eventually thromboprophylaxis in high-risk situations might be enough to prevent most VTE, regardless of inherited thrombophilia status.

Screening has been recommended for adolescents at fertile age with a family history of thrombosis and/or thrombophilia before start of oral contraceptives (34). Combined oral contraceptives are an important risk factor for VTE. The thrombotic risk is much

TABLE 1 | Association-inherited thrombophilia with risk of VTE in children.

	Prevalence (%) (population)	Summary OR (95% CI) first VTE (19)	Summary OR (95% CI) recurrent VTE (19)	Annual risk (%, 95% CI) for recurrence after non-CVC-related VTE (31)	Annual risk (%, 95% CI) for VTE in asymptomatic carriers[a] (32)
Antithrombin deficiency	0.02	8.73 (3.12–24.42)	3.37 (1.57–7.20)	5.4 (2.6–10)	2.82 (1.63–4.80)
Protein C deficiency	0.2	7.75 (4.48–13.38)	2.53 (1.30–4.92)	1.3 (0.3–3.8)	
Protein S deficiency	0.03–0.13	5.77 (3.07–10.85)	3.76 (1.57–8.04)	0.7 (0.08–2.4)	
Factor V Leiden	3–7	3.56 (2.57–4.93)	0.77 (0.40–1.45)		0.25 (0.12–0.53)
Prothrombin mutation	1–2	2.63 (1.61–4.29)	2.15 (1.12–4.10)		0.42 (0.17–1.01)

[a]*First- or second-degree relative of pediatric patient with venous thromboembolism (VTE) and thrombophilia.*
OR, odds ratio; CI, confidence interval; CVC, central venous catheter.

higher in women with high-risk than with low-risk thrombophilia. The annual thrombotic risk on combined oral contraceptives is 4.3% for asymptomatic carriers with a positive first-degree relative with VTE and high-risk thrombophilia. The risk is only 0.2–0.5 per year of use for asymptomatic carriers with a positive first-degree relative with VTE and low-risk thrombophilia (35). As a consequence, it may be worthwhile to test adolescents from families with high-risk thrombophilia to avoid use of combined contraceptives. However, in case of strong family history for VTE, combined contraceptives should be avoided in asymptomatic carriers of low thrombophilia, as well. When counseling these patients, it is important to realize that in families with a family history for VTE and/or thrombophilia, the thrombotic risk is also increased in unaffected relatives, due to yet unknown genetic variables and/or clinical risk factors (35). Consequently, negative thrombophilia testing may cause false reassurance. Therefore, some guidelines advise to consider an alternative contraceptive in women with a first-degree relative with VTE, independent of testing (36).

DISADVANTAGES OF TESTING

One of the disadvantages of testing children with VTE could be the psychological stress of knowing to be a carrier of an inherited thrombophilic defect. No studies are available investigating the psychological impact of thrombophilia testing on children. In adults, thrombophilia testing does not seem to trigger psychological stress or worry (37, 38). Another disadvantage may be the potential problems with health insurance or life insurance in future. One of the patients in the study of Bank et al. had been discriminated by an insurance company because of FVL. The other 16 patients had not informed the insurance companies (39). Finally, thrombophilia testing is expensive. Many tests are ordered inappropriately (40, 41). Proper thrombophilia testing will reduce costs.

WHO SHOULD WE TEST FOR INHERITED THROMBOPHILIA IN CHILDREN WITH A FIRST THROMBOTIC EVENT?

As mentioned before, the chance of finding inherited thrombophilia varies between pediatric patient groups with VTE. Inherited thrombophilia seems to be present in adolescents with unprovoked thrombosis and children with a positive family history. In the study of Revel-Vilk et al., thrombophilia was detected in only 13% of all 171 pediatric patients with VTE, but in 60%

TABLE 2 | Arguments pro and contra thrombophilia testing in children with venous thromboembolism (VTE).

Arguments pro thrombophilia testing	Arguments contra thrombophilia testing
Association between inherited thrombophilia and VTE in children	
Explanation of pathophysiology, especially if VTE was unprovoked	Most pediatric patients have at least one clinical risk factor, illustrating that a thrombophilic defect alone is not enough to develop VTE
	It is unclear whether the association is valid for all patients groups, for example, children with catheter-related thrombosis
Management of VTE in children	
Prediction of recurrence risk and opportunity for prophylactic anticoagulation in high-risk situations, especially in patients with antithrombin deficiency	All children should get prophylactic anticoagulation in high-risk situations after first VTE
	Efficacy of prophylactic strategies have not been studied in children
Identification of asymptomatic relatives with inherited thrombophilia	
Instruction about signs and symptoms of VTE to accelerate diagnosis and avoidance of thrombotic risk factors, such as obesity and smoking	Testing is not necessary to instruct patient and family members about signs and symptoms of VTE and to avoid thrombotic risk factors
Opportunity for prophylactic anticoagulation in high-risk situations, especially in patients with high-risk thrombophilia	As most VTE in affected family members are provoked, thromboprophylaxis in high-risk situations might be enough to prevent VTE
Counseling about combined oral contraceptives in asymptomatic female carriers with thrombophilia	False reassurance if thrombophilia testing is negative
	Consider alternative contraceptive in all women with first-degree relative with VTE, without testing
	In general: psychological distress of knowing to be a carrier and difficulties to obtain health or life insurances

of the adolescents with unprovoked thrombosis (22). Ruud et al. showed in a cross-sectional study that a positive family history for VTE increased the relative risk of a child having inherited thrombophilia to 2.35 (95% CI, 1.1–5.2) (42). In addition, in a prospective cohort study of 100 neonates and children with VTE, positive family history appeared to be the only predictor for presence of inherited thrombophilia (OR 14.9; 95% CI, 1.9–113) (24). In neonates and children with catheter-related thrombosis, thrombophilia was found less frequently. For example, Salonvaara et al. described 10 neonates with symptomatic catheter-related thrombosis. Only 1 of the 10 patients had FVL (26). Albisetti et al. studied the prevalence of thrombophilia in cancer patients with and without catheter-related thrombosis. Thrombophilia was found in 4% of cancer patients with VTE and in 12% of patients without VTE (21). Finally, Thom et al. could not find an association between catheter-related VTE and thrombophilia in cardiac pediatric patients (23).

So, thrombophilia testing seems to be advisable in adolescents with unprovoked VTE and in children with a positive family history for VTE and less useful in neonates and children after a first episode of catheter-related VTE.

SUMMARY

The presence of inherited thrombophilic defects in neonates and children with a first event of VTE does not influence primary antithrombotic management and while it may be one of the causes of the thrombotic event, it infrequently alters long-term management. However, the presence of antithrombin deficiency with its high risk of recurrent thrombosis may warrant adjustment of long-term management. In these children, intermittent anticoagulation in high-risk situations may aid to prevent recurrent thrombotic episodes. Furthermore, testing might be helpful to identify asymptomatic female relatives with thrombophilia who may get better informed about a healthy lifestyle and the risks of combined oral contraceptives at fertile age.

On the other hand, one might argue that all children with first VTE are candidates for prophylactic anticoagulation in high-risk situations, not only antithrombin deficient children. And a positive family history for VTE might be enough to choose less thrombotic contraceptive methods, such as progesterone-only preparations (**Table 2**).

Consequently, testing for inherited thrombophilia in children with a first episode of VTE should not be performed on a routine basis. In neonates and children with catheter-related thrombosis, inherited thrombophilia seems to contribute less to the thrombotic event than in adolescents with unprovoked thrombosis and children with a positive family history for VTE. Therefore, especially these latter groups seem candidates for testing.

In these children, the decision of testing should be made on an individual base after proper counseling before and after testing by an experienced physician, discussing the disadvantages and benefits of testing, the preference of the patient, and the consequences of the test results after testing.

AUTHOR CONTRIBUTIONS

CO and UN-G were both involved in drafting the concept of the manuscript. CO wrote the manuscript, UN-G read, edited, and approved final manuscript.

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The Impact of Central Venous Catheters on Pediatric Venous Thromboembolism

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The use of central venous catheters (CVCs) in children is escalating, which is likely linked to the increased incidence of pediatric venous thromboembolism (VTE). In order to better understand the specific risk factors associated with CVC-VTE in children, as well as available prevention methods, a literature review was performed. The overall incidence of CVC-VTE was found to range from 0 to 74%, depending on the patient population, CVC type, imaging modality, and study design. Throughout the available literature, there was not a consistent determination regarding whether a particular type of central line (tunneled vs. non-tunneled vs. peripherally inserted vs. implanted), catheter material, insertion technique, or insertion location lead to an increased VTE risk. The patient populations who were found to be most at risk for CVC-VTE were those with cancer, congenital heart disease, gastrointestinal failure, systemic infection, intensive care unit admission, or involved in a trauma. Both mechanical and pharmacological prophylactic techniques have been shown to be successful in preventing VTE in adult patients, but studies in children have yet to be performed or are underpowered. In order to better determine true CVC-VTE risk factors and best preventative techniques, an increase in large, prospective pediatric trials needs to be performed.

Keywords: central venous catheter, pediatric, venous thromboembolism, venous thrombosis, thromboprophylaxis, tunneled line, peripherally inserted central catheter

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INTRODUCTION

Central venous catheters (CVCs) are the single largest risk factor for pediatric venous thromboembolism (VTE) in all pediatric populations. The incidence of VTE in children is increasing, most likely secondary to advances in care of critically ill children and the increased insertion rate of CVCs (1). The use of CVCs has risen over the past decade due to their relative ease in placement and necessity for many lifesaving treatments, but this increase will likely lead to further escalating rates of pediatric VTE. CVCs can lead to VTE by causing vascular injury during insertion, as well as causing turbulent blood flow while the catheter is laying in the vessel lumen, with 85% of pediatric VTEs being CVC related (2, 3). Studies have been performed to evaluate catheter types, insertion locations, and catheter sizes that may lead to the highest probability of VTE. Most studies focus on limited patient populations, such as infants and patients in the intensive care setting or malignancy. Unfortunately, at this time, there are no guidelines in pediatric patients on how to choose the best central catheter type or insertion technique or prevention modalities to decrease the occurrence of VTE. CVC failures may be attributed to chemical or mechanical obstructions or VTE. This manuscript will review

the current knowledge of risk factors regarding CVC-associated VTEs and thromboprophylactic interventions in order to provide the first steps toward creating guidelines to prevent thrombosis.

METHODS

Search Strategy

We identified English articles using Medline (1975–August 2016) and Scopus (1975–August 2016). The search strategies comprised "venous thromboembolism," "risk," "children," central venous line, central venous catheter, and venous access device, with multiple subject headings and text words per concept. Selectively exploding subject headings, with relevant subcategories, permitted ever-increasing specificity. We included systematic reviews, meta-analyses, randomized controlled trials, prospective cohorts, and retrospective cohorts. Case reports and case series were excluded.

Study Selection

We excluded studies of patients older than 21 years based on the definition of pediatric age from the National Institute of Child Health and Human Development. For studies that included pediatric and adult patients, we excluded those without clear sub-analyses for patients under 21 years. Similarly, we excluded studies on arterial thromboembolism unless cases of VTE were included and clearly delineated in sub-analyses. Studies were identified as narrative reviews, commentaries, single case reports, retrospective case series, cross-sectional studies, case–control studies, cohort studies (retrospective and prospective), registry studies, or clinical trials, the first three of which were excluded.

This review included only pediatric CVC-related VTE with an aim to identify additional risk factors and populations at risk. An overview of the literature regarding different types and locations of CVCs, populations at risk, and prophylactic mechanisms will be discussed.

RESULTS

CVC Data

Incidences of CVC-VTE in children reported in the literature vary largely, ranging between 0 and 74% for patients with CVCs (4). This variation is explained by differences in study design and characteristics of the study populations, such as age, underlying diseases, purpose of the CVCs, and use of prophylactic anticoagulation. Most importantly, reported incidences of CVC-VTE depend on clinical awareness and the diagnostic test used to investigate for VTE. Incidences of CVC-VTE in children identified through clinical diagnosis were 4–13% (5–7), through venous ultrasonographic screening were 1–44% (5), and screening *via* venography were 13–50% (6–8). **Table 1** highlights CVC characteristics that may lead to an increased VTE rate.

TABLE 1 | Characteristics of CVC that may cause an increased incidence of VTE in children.

CVC characteristic associated with increased VTE incidence	Reference
Externally tunneled CVCs (vs. internal CVCs, such as port-a-caths)	(9)
CVCs placed in the femoral vein (vs. upper extremity)	(10, 11)
CVCs placed on the upper left side, in the subclavian vein (vs. jugular), and percutaneous technique (vs. cut-down)	(11, 12)
Peripherally inserted central catheters (vs. tunneled lines)	(13)
Increased time CVC is in place, especially over 4 years	(14)
Multi-lumen CVC (vs. single lumen)	(15)
Polyurethane CVC material (vs. silicone estomer)	(16)
Blind approach technique for insertion (vs. ultrasound guidance)	(17)

CVC, central venous catheter; VTE, venous thromboembolism.

CVC Types and Insertion Locations

There are three distinct types of catheters: non-tunneled, which includes peripherally inserted central catheters (PICCs) and acute short-term lines; tunneled (Broviacs and Hickmans); and totally implanted CVCs (port-a-caths). The ideal type of CVC to minimize CVC-VTE is unknown. Although the populations described in systematic reviews and meta-analyses are heterogeneous in terms of patient location [e.g., neonatal or pediatric intensive care unit (ICU)] or underlying diagnoses (e.g., malignancy, sepsis), identification of additional risk factors (risk stratification) has not been carried out. As a result, determining the sole impact of the catheter type/location to the development of CVC-VTE is challenging. Furthermore, differing statistical analysis within studies of similar patient cohorts makes comparison of results across studies challenging. In a systematic review, 15,979 children with CVC were reviewed (18). Of all locations of CVCs implanted, the incidence of thrombosis was 1.7% [95% confidence interval (CI): 0.8–2.8]; however, the highest incidence was in umbilical CVCs 3.7% (CI: 0–12.2) and non-tunneled CVCs 3.7% (CI: 0–11.1). The lowest incidence of CVC-VTE was in tunneled lines [0.6% (CI: 0.2–1.2)] (18). In contrast, a meta-analysis by Vidal et al. (19), the frequency of thrombosis per 1,000 catheter days demonstrated PICCs, umbilical, and non-tunneled catheters as having the lowest frequency of CVC-VTE, 0.14–0.18, and tunneled catheters having the highest frequency, 0.28. The frequency of CVC-VTE was similar in the upper, 0.24 (CI: 0.17–0.31) and lower extremities, 0.2 (CI: 0.13–0.27) (19), although a trend toward increased CVC-VTE in femoral and subclavian insertion is reported with a recommendation for jugular vein insertion (11).

CVC Composition and Insertion Technique

There are varied catheter compositions, although polyurethane and silicone elastomer is typically used, with silicone catheters reported to be the least thrombogenic (16). There was no difference between antibiotic-impregnated or heparin-bonded catheters in the incidence of CVC-VTE (20). With respect to CVC diameter and patient age, there are conflicting relationships reported between jugular diameter and patient height, weight, age, and body surface area (21). The use of a 6Fr/2 mm CVC in patients <1 year of age was associated with complications in one study (22). Multiple lumen catheters are associated with increased occurrence of CVC-VTE, which may be due to the larger size of multi-lumen CVCs vs. a single lumen CVC (15, 23).

In terms of insertion technique among adults, ultrasound-guided approach vs. blind approach to line insertion resulted in decreased complications (17). Although not well defined,

experts recommend ultrasound-guided approach to line insertion (24–26). In a pediatric study of patients with acute lymphoblastic leukemia, a percutaneous insertion technique was shown to have an increased incidence of CVC-VTE over cut-down technique (12).

Patient Data

Venous thromboembolism in children can also occur as a secondary complication of severe primary diseases (**Table 2**). The most important exogenous risk factor is the presence of a CVC. Mahajerin et al. completed a systematic review and meta-analysis of risk factors and risk assessment models using case–control and non-case–control studies identifying five independent risk factors for VTE in pediatric hospitalized patients (27). The most significant risk factor for all hospital-acquired VTE (HA-VTE) was a CVC presence, followed by the following populations: those with systemic infection, ICU admission, mechanical ventilation, and prolonged hospital stay. HA-VTE was more prevalent in males than females (0.55) in non-case–control studies, which is consistent with the results found by Raffini et al. in the Pediatric Health Information System Data Base (1). Additionally, there is a bimodal age pattern in pediatric patients, revealing a peak incidence in neonates and then the adolescent age group. CVC-VTEs are more likely to occur in neonates, whereas non-CVC-VTEs are more likely to occur in adolescents (28). Populations reported to be at the highest risk for CVC-VTE include those with malignancy, sickle cell disease, congenital heart disease (CHD), chronic total parental nutrition (TPN) use, and trauma. Other patients shown to be at an increased risk for CVC-VTE are those with metabolic disorders, renal disorders such as nephrotic syndrome and kidney failure requiring dialysis, and those with cystic fibrosis (28–30). We will discuss in detail those at the highest risk for CVC-VTE.

Children with Hematologic and Malignant Disease

The pathogenesis of thrombosis in patients with cancer is multifactorial. This includes the affect of the disease, in which tumor cells interfere with the hemostatic system by secreting procoagulant molecules and cytokines, as well as the invasion or compression of blood vessels my malignant cells (29). Chemotherapeutic agents are also highly thrombogenic, including asparaginase, which causes antithrombin deficiency and steroids which increase factor VIII/von Willebrand factor complex (30). However, the most important risk factor is the presence of a CVC, which is composed of thrombogenic material and obstructs venous flow and irritates the vessel wall (31). In a single-center study, children with malignancy and a port-a-cath, younger age, female sex, prolonged duration of a port-a-cath, and a left-sided device were independent risk factors for CVC-VTE (32).

Sickle cell disease has been demonstrated to have features associated with hypercoagulability, including increased levels of endothelial and platelet microparticles (33). Patients with sickle cell disease also have long-term CVCs, multiple hospitalizations, infections, and need for surgeries, thus increasing their risk for VTE. However, the reported incidence in retrospective studies for CVC-VTE is 0.2%, less than other high-risk populations (34, 35).

TABLE 2 | Disease states that lead to an increased rate of CVC-associated venous thrombosis in children.

Primary disease states with an increased VTE incidence
• Malignancy with any type of CVC. For patients with a port-a-cath: increased risk in younger females with left-sided CVCs placed for a prolonged duration
• Neonates in an intensive care unit
• Critically ill children, especially those with a CVC-associated bloodstream infection or requiring mechanical ventilation
• Congenital heart disease
• Systemic infection
• Intestinal failure requiring total parental nutrition
• Trauma, especially those with a high injury severity score, received a blood product transfusion or an adolescent

VTE, venous thromboembolism; CVC, central venous catheter.

Critically Ill Neonates and Children

In a recent review, Park et al. reported an incidence of 9.2% of CVC-VTE in patients in the neonatal ICU (36). Alternatively, the rate of CVC-VTE was found to be 1.4 per 1,000 hospitalized neonates with CVC being an independent risk factor with a 0.9% risk (15). Fifty percent of children in PICUs have a CVC with a reported incidence of 0.8% symptomatic VTE (37). Children with CVC-VTE in the PICU had a median of 1 additional risk factor in addition to having a CVC (37), with catheter-associated blood stream infection being the most common presenting symptoms of CVC-VTE (38). Higgerson et al. in a prospective study with 11 pediatric ICUs identified other independent risk factors for thrombosis including mechanical ventilation and odds ratio (OR) 2.8 (CI: 0.98–7.93) (3).

Children with CHD

Children with CHD often have disruptions in the balance of hemostasis, which paradoxically could result in bleeding, thrombosis, or both. Cyanotic CHD is more commonly reported to have known hemostatic abnormalities compared with acyanotic CHD. Reported differences include abnormalities in coagulation proteins, platelets number and function, and red cell number and function altering hemostasis. These abnormalities can result in bleeding and/or thrombosis, with many having >1 abnormalities present (39). The reported incidence of symptomatic and asymptomatic CVC-VTE in children with CHD and CVC is 28% (40). Superior vena cava syndrome resulting from CVC-VTE is a serious consequence for children with CHD inhibiting further surgical palliation and may be life threatening.

Children with Systemic Infection

Systemic infection has been identified as an additional risk factor in all high-risk populations, although no studies have specifically evaluated systemic infection and CVC-VTE. However, in severe sepsis, dysregulation of the hemostatic system may lead to disseminated intravascular coagulation and result in micro-vascular thrombosis that may contribute to CVC-VTE (41). In addition, sepsis has been associated with the development of neutrophil extracellular traps (NETs), which are composed of extruded chromatin, which is negatively charge. The NETs are responsible

for killing micro-organisms but have also been found to be highly prothrombotic (42). More studies in this area are needed.

Children with Intestinal Failure

One retrospective study reported 53 children with intestinal failure (43). Thirty subjects had venous imaging, and 57% of the imaged children had at least one symptomatic CVC-VTE with a mean of 5.6 ± 3.8 (range 1–12) CVCs per patient. CVC failure occurred in 53% of subjects, but there was not a significant difference in VTE rates in subjects who had a catheter occlusion or bloodstream infections and those that did not. By contrast, another study evaluating children on home TPN with inflammatory bowel disease were reported to only have an incidence of CVC-VTE of 10% (44).

Children after Traumatic Injury

The presence of a CVC continues to be the single greatest risk factor for VTE in pediatric trauma patients (OR 64, CI: 68.8–243.9) with a reported incidence of 0.2% for symptomatic CVC-VTE (45). Sixty-seven percent of VTE in trauma patients is at the site of the CVC (46). The combination of older age and increased injuries (increased injury severity score) escalate the risk of CVC-VTE (45). Consideration may be given to blood product transfusion, which is also reported to increase VTE in trauma patients (47). A recent study from the National Trauma Databank demonstrated that VTE risk increases in children beginning at age 13 and peaks at age 16, increasing to an incidence of 1% at age 16, independent of other VTE risk factors (47, 48).

CVC-Related VTE Prevention

There are two main categories of prophylactic measures for children who are at risk for a CVC-VTE. These include mechanical prophylaxis, which consists of graduated compression stockings (GCSs) or intermittent pneumatic compression devices (IPCs), and pharmacological prophylaxis, such as systemic anticoagulation, ethanol locks, or fibrinolytics.

Mechanical Prophylaxis

Graduated compression stockings and IPCs improve venous blood return from the lower extremities by providing circumferential or intermittent pressure. Theoretically, the use of GCSs and IPCs may not prevent CVC-VTEs, especially in the upper extremity where many CVCs are placed, but there could be some benefit by improving overall venous blood flow and activating systemic fibrinolysis (49). Many children will not have access to mechanical prophylaxis due to size constraints of the devices. Unfortunately, studies have not been conducted in pediatric patients to determine if either modality is beneficial, but systematic reviews in adults have shown that both the use of GCSs or IPCs can prevent VTE (50, 51).

Thromboprophylaxis

Studies regarding the efficacy and safety of prophylactic anticoagulation in pediatric patients are limited. Meta-analysis on the use of antithrombotic agents (unfractionated heparin, low molecular weight heparin, warfarin, and antithrombin concentrate) and nitroglycerin did not demonstrate any significant efficacy with prophylaxis of CVC-VTE, although the studies were underpowered and closed early due to poor accrual (19).

Ethanol Locks

Ethanol lock therapy has been demonstrated to decrease the rate of central venous line-associated blood infections (CLABSI) in a number of pediatric populations with CVC. There are no anticoagulant properties associated with ethanol; however, ethanol decreases infection and there may be an interrelationship between bacteremia and CVC-VTE (52).

Lytic Locks

Tissue plasminogen activator (TPA) is the main fibrinolytic drug used for clot lysis and restoration or maintenance of catheter patency. A literature review focusing on pediatric patients with CVCs and the use of TPA revealed that 50–90% of catheters were cleared of thrombosis when TPA was instilled, with improved efficacy when doses where higher and dwell times were longer (53). Unfractionated heparin has also been used to maintain and improve catheter patency. A prospective cross-over controlled trial compared TPA to UFH in preventing CVC-VTE in patients receiving dialysis found TPA to be superior for VTE prevention (54).

SUMMARY

Venous thromboembolism is a serious and potentially life-threatening condition that has lead to increased morbidity and mortality in pediatric patients. CVCs remain a predominant risk factor for VTE in children, and their use and rate of insertion continue to climb. Data evaluating the incidence and specific risk factors for CVC-VTE with various CVC types and medical conditions are limited. Most studies are predominantly retrospective, single institution, and focused on a single central catheter type. This article sought to provide a brief review of the literature regarding pediatric CVC-related VTE in order to highlight various risk factors linked to catheter characteristics and the patients' medical history.

The overall incidence of CVC-VTE in pediatrics varies greatly due to differences in patient population, catheter type, detection methods (screening vs. requiring clinical symptoms), and imaging modality. CVC type and its effect on VTE incidence remain the most significant question. PICCs, which are usually placed into vessels of smaller caliber with a longer intravascular course, are being placed even more readily than other forms of CVCs (55). Therefore, truly understanding the VTE risk associated with PICCs vs. other CVCs is of great importance. Although the study results vary, increased CVC-VTE incidence has been found with externally tunneled CVCs over implanted CVCs, PICCs and umbilical lines over tunneled lines, CVCs placed in the subclavian and femoral vein, lines placed in the upper left side, multi-lumen CVCs, lines inserted without ultrasound guidance, and CVCs made from polyurethane over silicone.

Various patient populations have been shown to have an increased risk of VTE. There is difficulty determining if these

populations are more at risk for VTE overall or CVC-related VTE specifically. Children with the highest risk of CVC-VTE are those with malignancy, systemic infection, CHD, gastrointestinal failure, sickle cell disease, those in an ICU, and those with a traumatic injury. Besides having a CVC, some of these patients have many other compounding risk factors, such as being in an inflammatory state, having decreased mobility, and being exposed to thrombogenic medications such as steroids or asparaginase.

Preventative measures, such as mechanical or pharmacological prophylaxis, have not been largely studied in pediatric patients, and thus, their utility in CVC-VTE prevention is unknown. Recurrent TPA locks have been shown to improve catheter flow in patients with CVCs obstructed by thrombosis.

In conclusion, our review illustrates the need for large prospective pediatric studies to truly evaluate catheter types, insertion techniques, and clinical characteristics to create guidelines for our patients prior to receiving a CVC. We hope that this review of the current literature will lead to a better understanding of the risk factors linked with CVC-VTE, which will promote the needed prospective evaluation.

AUTHOR CONTRIBUTIONS

JJ assisted in writing and editing the manuscript. MB assisted in performing the review and writing the manuscript. PM assisted in performing the review and writing and editing the manuscript. JJ and PM addressed the reviewer comments.

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Venous Thromboembolism in Critical Illness and Trauma: Pediatric Perspectives

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Critically ill children and those sustaining severe traumatic injuries are at higher risk for developing venous thromboembolism (VTE) than other hospitalized children. Multiple factors including the need for central venous catheters, immobility, surgical procedures, malignancy, and dysregulated inflammatory state confer this increased risk. As well as being at higher risk of VTE, this population is frequently at an increased risk of bleeding, making the decision of prophylactic anticoagulation even more nuanced. The use of pharmacologic and mechanical prophylaxis remains variable in this high-risk cohort. VTE pharmacologic prophylaxis is an accepted practice in adult trauma and intensive care to prevent VTE development and associated morbidity, but it is not standardized in critically ill or injured children. Given the lack of pediatric specific guidelines, prevention strategies are variably extrapolated from the successful use of mechanical and pharmacologic prophylaxis in adults, despite the differences in developmental hemostasis and thrombosis risk between children and adults. Whether the burden of VTE can be reduced in the pediatric critically ill or injured population is not known given the lack of robust data. There are no trials in children showing efficacy of mechanical compression devices or prophylactic anticoagulation in reducing the rate of VTE. Risk stratification using clinical factors has been shown to identify those at highest risk for VTE and allows targeted prophylaxis. It remains unproven if such a strategy will mitigate the risk of VTE and its potential sequelae.

Keywords: venous thromboembolism, deep vein thrombosis, pediatric critical illness, pediatric trauma, child, prophylaxis

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INTRODUCTION

Venous thromboembolism (VTE) diagnosis in hospitalized children appears to have increased markedly over the past decade (1). Critically ill and/or severely injured children are at a disproportionately higher risk of VTE events due to the presence of multiple VTE risk factors (2, 3). Clinical diagnosis of VTE can be especially challenging in a critically ill and severely injured child as extremity swelling and erythema may be non-specific signs and self-reporting of pain is limited by sedation, immobility, and physical state. Hence, a high degree of suspicion is needed on the part of a clinician to perform imaging and diagnose VTE.

In critically ill and injured adults, mechanical and pharmacologic prophylaxis is an accepted practice to mitigate VTE (4); however, this is not the case in children. In addition, VTE risk prediction and stratification remains a challenge and robust risk scoring systems remain elusive in children. Even if one were to develop the perfect risk screen, there are no data showing a benefit from prophylaxis in critically ill children. Despite the paucity of evidence surrounding screening and prophylaxis, health-care providers are motivated to develop strategies to reduce the incidence of VTE in children. While mechanical prophylaxis is relatively risk free, pharmacologic prophylaxis may increase the bleeding risk in this group of patients. This review will summarize the epidemiology/incidence and current controversies in regards to VTE in critically ill and severely injured children.

INCIDENCE AND RISK FACTORS FOR VTE IN CRITICALLY ILL OR INJURED CHILDREN

An increase in the diagnosis for VTE has been reported for hospitalized children from 2001 to 2008 (1); however, it is not known if this increase is equivalent among the subpopulations of critically ill or injured children. The interpretation of reported rates of VTE is confounded by the lack of standard VTE screening or for diagnosis of VTE. The reported incidence of VTE in critically ill and/or severely injured children is summarized in **Table 1**. There is a wide variation in incidence based on the study design and the specific population included. For instance, the incidence of VTE in pediatric trauma ranges from 0.2 to 0.5% in large, retrospective studies of hospitalized children using databases (5–10), while higher rates of 0.9–1.1% were found in smaller studies using data from the patient records (11, 12). For injured children admitted to the intensive care unit (ICU), the incidence rate (0.3–6.2%) is higher especially in prospective studies (3, 13–15).

For the general pediatric ICU population, the incidence of VTE ranges 0.3–0.9% (16–22), with the higher incidence being reported from prospective studies. Specific subpopulations of critically ill children report higher incidence of VTE including those with central venous catheters (CVCs) (17–19), cardiac disease (20, 21), and bacteremia (22).

The risk factors for VTE in critically ill and/or severely injured children are summarized in **Table 2**. Critically ill and/or severely injured children are at a disproportionately higher risk of VTE events than any other cohort of children due to the presence of multiple risk factors: including endothelial injury from trauma, CVC placement, and/or operative procedures; alterations in blood flow from immobility and poor perfusion requiring inotropic support; and hypercoagulability from sepsis, trauma, blood transfusion, or other dysregulated inflammatory states (see **Table 2**). The exact contribution of each of these factors is unclear; however, the presence of a CVC is probably the most important risk factor for VTE in this cohort of children. Most, but not all, studies found increasing age to be a risk factor for VTE in injured and critically ill children (see **Table 2**). In studies that performed a separate analysis for infants, <1 year of age was also associated with increased risk. For trauma patients, the risk of VTE appears to increase with higher injury severity scores (ISS) (see **Table 2**).

TABLE 1 | Incidence of VTE in critically ill or injured children.[a]

Reference	Design/data source	Population	VTE (*N*/total)	VTE incidence (%)
Allen et al. (11)	Retrospective, single center	Trauma	22/1,934	1.1
Connelly et al. (5)	Retrospective, NTDB data	Trauma	1,141/536,423	0.2
Yen et al. (8)	Retrospective, single center and NTDB data	Trauma	Single center: 49/17,366 NTDB 2011–2012: 1,168/281,248	0.3–0.4
Carpenter et al. (22)	Retrospective, single center	ICU (bacteremia)	21/229	9.2
Arlikar et al. (16)	Retrospective, single center, case-control, ICD-9 codes	ICU	57/19,000 (est)	0.3
Harris and Lam (10)	Retrospective, KID data	Trauma (TBI)	267/58,529	0.5
Al Tassan et al. (19)	Retrospective, single center	ICU (CVC)	21/248 CVC	8.5
Van Arendonk et al. (6)	Retrospective, NTDB data	Trauma	1,655/402,329	0.4
Faustino et al. (18)	Prospective, multicenter	ICU (CVC)	16/101	15.8
Askegard-Giesmann et al. (7)	Retrospective, multicenter, PHIS data	Trauma	671/260,078	0.3
O'Brien et al. (12)	Retrospective, multicenter, local trauma registries	Trauma	15/1,706	0.9
Hanson et al. (14)	Prospective, single center	Trauma, ICU	3/169	1.7
Greenwald et al. (30)	Retrospective, single center	Trauma	3/1,782	0.2
Hanson et al. (21)	Nested case–control, single center	ICU (cardiac disease)	41/1,070	3.8
Higgerson et al. (17)	Prospective, multicenter	ICU	62/6,653	0.9
O'Brien and Candrilli (13)	Retrospective, multicenter NTDB data	Trauma, ICU	1,087/135,032	0.8
Hanson et al. (15)	Nested case–control, single center	Trauma, ICU	9/144	6.2
Hanslik et al. (20)	Prospective, single center	ICU (CVC and cardiac disease)	25/90	27.8
Candrilli et al. (9)	Retrospective, multicenter, HCUP-KID data	Trauma	648/240,387	0.3
Cyr et al. (3)	Retrospective, single center, ICD-9 data	Trauma, ICU	11/3,291	0.3

[a]Age <21 years, includes only studies published since 2006 with defined incidence of VTE in pediatric ICU or in trauma populations.
NTDB, National Trauma Data Bank; TBI, traumatic brain injury; CVC, central venous catheter; KID, Kids Inpatient Database; PHIS, pediatric health information system; VTE, venous thromboembolism; ICU, intensive care unit.

TABLE 2 | Risk factors for VTE in critically ill or injured children.

Reference	Age (years)	CVC	Surgery	Illness/injury severity	Other risk factors
Allen et al. (11)	>13, OR 9.2	OR 4.4	Orthopedic, OR 6.8	N/A	MVI, OR 15.4
Harris and Lam (10)	>15, OR 3.7	OR 3.0	Orthopedic, OR 2.44 Cranial, OR 1.78	N/A	Ventilator, OR 1.9 Tracheostomy, OR 2.3 NAT, OR 2.8
Yen et al. (8)	13–15, OR 3.81 >16, OR 5.22	N/A	OR 8.0	ISS 9–15, OR 4.1 ISS 16–24, OR 10.8 ISS > 25, OR 15.7	GCS < 9, OR 2.8 Transfusion, OR 2.8
Carpenter et al. (22)	NS	NS	N/A	N/A	CRP > 20, OR 4.2 Hg nadir < 9, OR 5.2
Connelly et al. (5)	13–15, OR 1.3 16–17, OR 1.7	OR 1.9	OR 4.5	N/A	ICU, OR 5.5 Ventilator, OR 2.6 GCS < 9, OR 1.4 Pelvic/LE fx, OR 1.4
Arlikar et al. (16)	NS	OR 26	NS	N/A	Infection, OR 3.4
Van Arendonk et al. (6)	13–15, OR 2.0 >16, OR 3.8	OR 1.3	OR 3.8	ISS 9–15, OR 3.9 ISS 16–24, OR 5.9 ISS > 25, OR 7.2	Ventilator, OR 2.5 Transfusion, OR 1.5 GCS < 9, OR 1.3
Faustino et al. (18)	>13, OR 14.1	All	Postop-NS	PIM2-NS	
Askegard-Giesmann et al. (7)	N/A	OR 8.0	N/A	N/A	ICU OR, 3.7 Pelvic fx OR, 1.6
Hanson et al. (21)	NS	OR 1.1	N/A	PRISM3-NS	Single ventricle, OR 11.2
Higgerson et al. (17)	N/A	OR 9.3	N/A	N/A	
O'Brien and Candrilli (13)	<1, OR 1.75 14–17, OR 2.34	OR 1.8	Cranial, OR 1.8 Open LE, OR 1.1 Vascular, OR 2.8	N/A	TBI, OR 1.33 LE fx, OR 1.8 Pelvic fx, OR 1.2
Hanson et al. (15)	NS	OR 19	N/A	NS	PN, OR 20.8 NMB, OR 10.0 Inotropes, OR 10
Candrilli et al. (9)	NA	NA	NA	ISS 9–15, OR 2.1 ISS 16–25, OR 2.5 ISS > 25, OR 3.5	
Cyr et al. (3)	15–18, OR 19.5	OR 64	Chest, OR 6.9	ISS > 8, OR 5.3	SCI, OR 37.4

OR, adjusted odds ratio; NS, not significant; NA, not analyzed; MVI, motor vehicle injury; ISS, injury severity score; NAT, non-accidental trauma; CRP, C-reactive protein; Hg, hemoglobin; CVC, central venous catheter; LE fx, lower extremity fracture; GCS, Glasgow Coma Scale; PIM2, paediatric index of mortality 2; PRISM3, pediatric risk of mortality score; TBI, traumatic brain injury; NMB, neuromuscular blockade; PN, parenteral nutrition; SCI, spinal cord injury; ICU, intensive care unit.

Overall interpretation and generalizability of data in regards to incidence and risk factors is limited, given the significant differences in the population included and study design. Several, recent, large studies in children have used diagnostic codes for the identification of VTE (5, 6). Using diagnostic codes for identification of pediatric VTE has a low specificity and sensitivity (23). Hence, misidentification of children with and without VTE could result in differences in incidence rates and risk factors. Likewise, studies with smaller numbers of patients may fail to identify significant risk factors. Despite these limitations in study populations and methodologies, the incidence of VTE appears to increase in patients with multiple risk factors, with the presence of a CVC being the most important risk factor in critically ill and/or injured patients. Certain subpopulations of critically ill children have a greater risk for VTE, with an incidence of VTE >1%.

PREVENTION OF VTE IN CRITICALLY ILL OR INJURED CHILDREN

Efforts for prevention of VTE in critically ill or injured patients hinge on early mobilization and the use of mechanical and/or pharmacologic prophylaxis. Mechanical prophylaxis includes the use of sequential compression devices (SCD) or graduated compression stockings, both of which are limited by size and cannot be used in smaller children and on injured extremities. There are no pediatric studies showing efficacy of mechanical prophylaxis in preventing VTE.

There is little evidence to guide the use of pharmacologic thromboprophylaxis in critically ill and injured children. Published pediatric guidelines are based on weak evidence and recommend against the use of pharmacologic prophylaxis except in children with cyanotic congenital heart disease,

dilated cardiomyopathy, cavopulmonary anastomosis, end-stage renal disease, and primary pulmonary hypertension (24). A recently published consensus of experts in regards to pediatric trauma recommended against prophylaxis in children <12 years of age and gave a strong recommendation for pharmacologic prophylaxis in patients with a history of VTE, while a weak recommendation for patients with CVCs (25). Given the lack of data, it is not surprising that there is a wide variation in thromboprophylactic practices in critically ill children as shown in the PROTRACT study (26). This global point-prevalence study clearly demonstrated that the use of both mechanical and pharmacologic prophylaxes was center dependent with a wide variation in the use of prophylaxis. Data were collected on the type of pharmacologic thromboprophylaxis used in the ICU including aspirin, low-molecular-weight heparin, IV unfractionated heparin (UFH), subcutaneous UFH, warfarin, and clopidogrel. Aspirin was the most commonly used agent (143 of 308 patients, 46.4%), primarily because of patients with congenital heart disease. LMWH, almost exclusively enoxaparin, was the next most commonly used agent (113 of 308 patients, 36.7%). Warfarin was rarely used in the ICU setting (26).

Critically ill and/or injured children represent a high-risk cohort for VTE, especially in the setting of CVCs, and may merit from thromboprophylaxis. This is especially true as patients approach adulthood wherein heparin-based prophylaxis regimens have been shown to be effective in preventing VTE in critically ill adults (4). Whether such strategies are of benefit in critically ill and/or injured children remain unproven. However, a standardized systematic approach to VTE prevention may result in a reduction in VTE. This was demonstrated in a single-center study in the setting of pediatric trauma where a reduction in incidence of VTE was noted after implementation of standardized thromboprophylaxis guidelines (14). Notably in this study, the reduced incidence of VTE was not associated with an increase in pharmacologic prophylaxis. The authors speculate that the decrease in VTE was a result of standardized, focused pharmacologic prophylaxis to those patients at high risk for VTE.

Pharmacologic prophylaxis should be instituted thoughtfully especially in patients at high risk for bleeding. There are minimal data on bleeding in the setting of pharmacologic prophylaxis for VTE in the critical care or trauma setting in pediatrics. In a multicenter review of trauma registry data to assess pharmacologic prophylaxis, the rate of major bleeding was 0.3% (12). However, single-center data demonstrated a higher rate of 4% in hospitalized pediatric patients receiving pharmacologic prophylaxis (27). A recent prospective observational study of hospitalized children receiving prophylactic anticoagulation showed a similar incidence of major bleeding especially in patients following orthopedic surgery (28). Taken together, the data demonstrate a low but definite risk of bleeding children receiving pharmacologic prophylaxis. Hence, it is imperative that any preventive strategy utilizing pharmacologic prophylaxis account for the bleeding risk, especially in a high bleeding-risk cohort, such as children who are critically ill or severely injured.

In summary, VTE prevention in critically ill and/or injured children needs a standardized approach with VTE risk stratification. Interventions should include early mobilization and removal of CVCs alongside mechanical and pharmacologic prophylaxes, especially in children >12 years of age.

PREDICTING VTE RISK IN CHILDREN AFTER TRAUMA

Recently, two scoring systems to predict the risk of VTE in children hospitalized after trauma have been developed (5, 8). Both studies used the National Trauma Data Bank to derive and validate the VTE risk score over similar time periods. The model from Connelly et al. had good performance with an area under the curve of 93–94% (5). This model incorporated 10 VTE risk factors: age (increased risk for <1 year and adolescence), sex, Glasgow Coma Scale (GCS), CVC, intubation, blood transfusion, ICU admission, major surgery, pelvic fracture, and lower extremity fracture. Varying points for each risk factor are summed for a total score. Categorical risk was assigned based on this score: low risk (VTE incidence <1%), medium risk (VTE incidence 1–5%), and high risk (VTE incidence >5%). The authors suggest a potential management strategy to implement screening ultrasounds and SCD for the medium-risk group, with the addition of pharmacologic prophylaxis for the high-risk group. By contrast, Yen et al. used a combination of local trauma registry data and the national trauma data bank for development and validation of a VTE risk score model with good performance as shown by the area under curve of 91% (8). The preferred model incorporates six risk factors, for which varying points are accumulated: older age, GCS, ISS, blood transfusion, intubation, and major surgery. CVC was not analyzed as a risk factor for the model. A score >17 is associated with VTE risk >2%, referenced as a threshold for prophylaxis.

These studies provide the framework to convert epidemiologic risk factors into tools clinicians can use to predict the overall VTE risk for their injured patient. Both studies recognize the limitations of the national trauma database: surveillance bias, no temporal association of risks (intubation, surgery, and transfusion) with the development of VTE, and the confounding effect of variable use of thromboprophylaxis. The rare occurrence of VTE in the overall hospitalized pediatric trauma population makes large database studies necessary to provide adequate power of associated risks, with the risks studied limited to those captured in the database. As injured children in the ICU have a higher VTE rate compared to the overall hospitalized children after trauma, this high-risk population may be appropriate to prospectively validate and refine an optimal VTE prediction tool.

FUTURE DIRECTIONS

The ever-increasing medical complexity of critically ill and injured children implies that the risk of VTE will continue to be present especially in the setting of CVCs. Hence, standardized risk prediction and stratification will be the key to implementing any thromboprophylactic strategy. Validation of risk prediction tools will be challenging given the low overall incidence for VTE in

children. Currently, most risk assessment algorithms use clinical variables, and whether the addition of biomarkers bolsters their performance remains unclear. A recent prospective study in critically ill children with CVCs showed an association between factor VIII activity and catheter-related thrombosis (29).

Even with the ideal risk prediction tool, the appropriate interventions to prevent VTE are unknown. Hence, there is a pressing need to evaluate the efficacy of interventions in preventing VTE in children, including pharmacologic or mechanical prophylaxis, early ICU rehabilitation, and increased mobility. Given the low incidence of VTE in children, focusing on the subpopulations of critically ill or injured children at highest risk for VTE, including those with CVCs, will optimize the results of any clinical trial.

AUTHOR CONTRIBUTIONS

RC and SH conceptualized and wrote the manuscript.

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MINI REVIEW
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Pulmonary Embolism in Children

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Pulmonary embolism (PE) in the pediatric population is relatively rare when compared to adults; however, the incidence is increasing and accurate and timely diagnosis is critical. A high clinical index of suspicion is warranted as PE often goes unrecognized among children leading to misdiagnosis and potentially increased morbidity and mortality. Evidence-based guidelines for the diagnosis, management, and follow-up of children with PE are lacking and current practices are extrapolated from adult data. Treatment options include thrombolysis and anticoagulation with heparins and oral vitamin K antagonists, with newer direct oral anticoagulants currently in clinical trials. Long-term sequelae of PE, although studied in adults, are vastly unknown among children and adolescents. Additional research is needed in order to provide pediatric focused care for patients with acute PE.

Keywords: pulmonary embolism, pulmonary artery thrombosis, children, deep venous thrombosis, pediatrics

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INTRODUCTION

Although first described almost two centuries ago by von Löschner (1), our knowledge of pediatric pulmonary embolism (PE) remains fragmented. These gaps in our knowledge are intensified by the infrequency of diagnosis of pediatric PE, thus limiting a standardized approach to investigative and management strategy. Hence, it is possible that the morbidity and mortality of undiagnosed PE in children may be underestimated. Historically, PE in children was thought to occur in the setting of infection, but it is becoming clear that PE is increasingly related to cancer, congenital heart disease, acquired and inherited thrombophilias, and central line placements (2). Early registries from Canada and the Netherlands providing national data indicate PE as a rare event among pediatric populations (3, 4). The incidence of venous pulmonary thromboembolism has been steadily increasing in children, as a consequence of longer survival of critically ill children, with conditions that predispose to thromboembolic disease, as well as the increased use of central venous catheters (5, 6).

Studies examining the incidence of PE in children report an incidence of 8.6–57 in 100,000 in hospitalized children, and 0.14–0.9 in 100,000 when studying the general population of non-hospitalized children (3, 7–10). The wide range of incidence in hospitalized children may be a manifestation of the often clinically silent nature of PE, misdiagnosis, more comprehensive reporting or a function of the biased population of a tertiary care center (7). The National Hospital Discharge Survey data from 1979 to 2001 yielded a population-based incidence of 0.49/10,000 patients/year (9). There appears to be a predilection of pediatric PE in infants and toddlers, with a second peak seen in teenagers (9). Black children are estimated to have an incidence 2.38 times higher than white children (9). However, it is likely that these numbers are underestimated due to the often silent nature of PE in children. This is corroborated by autopsy data, which shows discordant rates of PE based on clinical suspicion. In one study, the diagnosis was only considered in 15% of patients with PE (11). It is apparent that a high index of suspicion is mandated for timely and effective care for children with PE (12).

In this review, we aim to highlight the presentation, diagnostic work-up, treatment, risk factors, and follow-up of pediatric PE. We will also discuss emerging novel therapies and future directions of research in this field.

PRESENTATION

For almost one century, physicians have noted that PE may occur without the classic symptomatology among children (13). Unlike in adults, pediatric PE often appears clinically silent (2). On retrospective review of children with an eventual diagnosis of PE, however, symptoms or signs were often present but may have been missed resulting in misdiagnosis, such as pneumonia, exacerbation of heart failure, or malignancy (7, 10). The time to diagnosis of PE as compared to adults is often longer with mean time to diagnosis being as high as 7 days as reported in some studies (12). Therefore, keeping a high index of suspicion for PE in children is critical. The majority of cases in which an autopsy revealed PE did not have an ante-mortem diagnosis of PE (11). Classic symptoms when present include increased shortness of breath, pleuritic chest pain, hemoptysis, cough, and even syncope. Patients may present with tachycardia, tachypnea, and edema due to deep vein thrombosis (DVT), as well as signs of right heart failure (2, 14). In addition, patient symptoms may be thought to be related to other underlying medical conditions such as congenital heart disease or infection that often coincide and predispose the patient to PE, thus masking the diagnosis (2). This may often lead to delay in or misdiagnosis and potential additional serious consequences (7, 12, 14, 15). An underlying diagnosis of PE should be considered when patients are not improving on therapy especially in the setting of conditions known to predispose to PE (**Table 1**) (16). In adults, specific validated diagnostic prediction tools, such as the Wells' criteria (17), the Geneva score (18), and the pulmonary embolism rule-out criteria (PERC) (19), exist for diagnosis of PE (20, 21).

TABLE 1 | Risk factors to be considered in etiopathogenesis of pulmonary embolism (Virchow's triad).

1. Damage to the endothelium
   a. Central venous catheters
   b. Inflammation (lupus, inflammatory bowel disease, etc.)
   c. Systemic infection
   d. Antiphospholipid antibodies
2. Change in laminar flow
   a. Congenital or acquired heart disease
   b. Local anatomical causes (e.g., congenital anomalies of pulmonary arteries or after corrective heart surgery, e.g., Fontan surgery)
   c. Total parenteral nutrition
3. Thrombophilia

A. Acquired
   a. Nephrotic syndrome
   b. Cancer
   c. Medications e.g., L-asparaginase therapy
   d. Pregnancy or hormonal supplementation
   e. Antiphospholipid antibodies

B. Inherited
   a. Deficiency of anticoagulants, e.g., protein S, C, and antithrombin III
   b. Factor V Leiden, prothrombin gene variant, etc.
   c. Elevated homocysteine

These models combine patient clinical signs and additional risk factors to assess pretest probability for the diagnosis of PE in adults (10). In children such models have not been validated. One study conducted by Biss et al. evaluated the modified Wells simplified probability score in 50 children with PE and 25 PE negative control patients, as well as D-dimer values in 27 PE positive and 12 PE negative patients and found that D-dimer had a low diagnostic utility for PE in children (22). Recently, a single-center retrospective study was conducted by Lee et al. in children undergoing either D-dimer testing or radiologic evaluation (computed tomography or ventilation-perfusion scan) in the emergency department setting. The investigators evaluated the test characteristics of the Wells criteria and PERC low-risk rule. Among the 561 patients, 36 (6.4%) were eventually diagnosed with PE. The Wells criteria demonstrated a sensitivity and specificity of 86 and 60%, respectively. The sensitivity and specificity of the PERC were 100 and 24%, respectively. A clinical decision rule, including the presence of oral contraceptive use, tachycardia, and oxygen saturation <95%, demonstrated a sensitivity and specificity of 90 and 56%, respectively, a positive and negative likelihood ratio of 2.0 and 0.2, and a positive and negative predictive value of 0.12 and 0.99, respectively (23).

WORK-UP

Diagnostic tests for evaluation of PE can be divided into those needed for definitive diagnosis of PE (**Table 2**), tests that may aid in diagnosing the severity of PE (i.e., risk prediction and, thus, may help in decision making of management of PE) and miscellaneous tests that should be performed prior to anticoagulant therapy of PE.

Tests for Diagnosis of PE

Ventilation/Perfusion (V/Q) Scan (Radionuclide Scintigraphy)

Ventilation/perfusion scans have historically been used to test for diagnosis of PE in children. While safe and easy to perform, they are not guaranteed to provide a definitive diagnosis. V/Q mismatch can be seen in pneumonia, sickle-cell disease, arterial stenosis, and air, fat, and foreign body embolism (24).

In general, this testing is done using the radiotracer 99m-labeled macroaggregated albumin. Areas clear of radiotracer activity represent reduced blood flow. To reduce the rate of false-positives, patients are supine during injection. Imaging, preferably in eight views (bilateral anterior and posterior oblique, anterior, posterior, and bilateral lateral), is then completed with the patient upright. At the very least, in critically ill patients, one anterior and bilateral oblique views must be used. Due to the need for active aerosol inhalation, these tests are technically difficult for younger patients (25).

Victoria et al. describe six patients out of thirteen with PE who underwent V/Q scans to determine its presence and describe four patients to have a positive result. The remaining two patients had low probability results (26). The Canadian registry shows that PE was diagnosed in 22 of 31 children who had a high probability V/Q scan (3). This test appears to be less favored when compared to CT pulmonary angiography (CTPA). The major limitation

TABLE 2 | Advantages and disadvantages of diagnostic modalities and therapies.

Advantages and disadvantages of diagnostic tools and therapies in the management of pulmonary embolism in children		
Diagnostic Tool	**Advantages**	**Disadvantages**
Ventilation/perfusion scan	• Safe and easy to perform	• Low sensitivity • False-positives from other diagnosis • Difficult in younger patients • Technically demanding
CT pulmonary angiography	• Non-invasive • Short study time • Widely available • Identifies alternate thoracic etiologies	• May miss small peripheral emboli • Radiation exposure, particularly in young females • Contraindicated in renal insufficiency
Pulmonary angiography	• Gold standard • Generally diagnostic	• Invasive • Radiation exposure • May not be easily available
Magnetic resonance imaging/magnetic resonance pulmonary angiography	• No need for radiation or contrast • Can assess cardiovascular anatomy	• May miss small peripheral emboli • Long duration of examination • May not be easily available
Therapy	**Advantages**	**Disadvantages**
Unfractionated heparin (UFH)	• Short half-life • Reversal agent available	• Continuous intravenous infusion • Unable to administer outside of medical setting • Possible development of heparin-induced thrombocytopenia (HIT) • Frequent monitoring needed • Risk of bleeding
Low molecular weight heparin	• Easy to administer • Reversal agent available	• Effectiveness uncertain in obese patients • Possible pain with administration • Difficult to achieve therapeutic levels in infants • Possible development of HIT (less than UFH) • Risk of bleeding
Warfarin	• Oral • Able to monitor therapeutic level • Reversible	• Frequent monitoring • Difficult to maintain in therapeutic window in children • Multiple drug/food interactions • Risk of bleeding
Direct oral anticoagulant	• Oral • No frequent blood draws	• No way to monitor • Few reversal agents • Not approved for patients <18 years • Risk of bleeding

remains the fact that most patients have low or intermediate probability risk scans that are non-diagnostic (6).

CT Pulmonary Angiography

Due to its practicality, CTPA has rapidly overtaken V/Q scans as a primary imaging technique for diagnosis of PE. The speed, reliability, and ability to specifically detect other pathologies make this test ideal. In this modality, the criteria for acute PE include the presence of a sharply marginated complete or partial pulmonary arterial filling defect present on at least two consecutive images (25). Adult data show CTPA sensitivity of 83% (90% when done in combination with CT venography) and specificity of 95% (27). Similar data for/regarding children do not exist. Kritsaneepaiboon et al. (28) described a 9.3% false positive rate and a 2.4% false negative rate in pooled pediatric data from eight studies. The most critical disadvantages to this technique remain the exposure to ionizing radiation and insensitivity to small, sub-segmental emboli. New CT techniques are on the horizon to help mitigate some of these issues and increase the accuracy with reduced radiation. These include both imaging techniques, such as dual-energy CTA, and reconstruction algorithms, such as model-based iterative reconstruction and adaptive statistical iterative reconstruction. These reconstruction algorithms alleviate apprehension to radiation and are becoming more widely available. These reconstruction techniques provide the same anatomic detail as conventional scans (25).

Pulmonary Angiography

The traditional gold standard for diagnosis of PE, pulmonary angiography is invasive and expensive that limits its use in the pediatric population. This procedure includes weight-based injection of low-osmolar non-ionic contrast material through a pigtail catheter placed within the left or right pulmonary artery. The diagnosis is made when an intraluminal filling defect is recognized (25).

Magnetic Resonance Imaging/Magnetic Resonance Pulmonary Angiography (MRI/MRPA)

The elimination of ionizing radiation and use of safer contrast agents, make MRI/MRPA an attractive option for clinicians. Preliminary adult data show that MRI/MRPA may be a promising technique for those patients in whom CT is contraindicated (29). This topic is not extensively studied in children, so its effectiveness and reliability are uncertain in this patient population.

Tests That May Aid in Risk Assignment

The clinical severity of PE varies widely. Children with PE may be asymptomatic (i.e., PE may be detected incidentally during other investigative work-up) or may present with complete cardiovascular collapse. While in some children, treatment with standard anticoagulation may be the appropriate treatment, in others, additional interventions such as thrombolysis or surgical thrombo-embolectomy may be warranted. Thus, after diagnosis of PE, an attempt should be made to categorize the patients into specific risk categories that can predict adverse outcomes in children with PE. In adults, specific models exist for risk prediction of PE and patients are often categorized into high risk (presentation with cardiovascular collapse), intermediate risk (patients who are normotensive but show evidence of right heart strain either on electrocardiogram [EKG], echocardiography, or by biomarkers) and low risk (symptomatic but absence of preceding features) (30, 31). Unfortunately, such risk categorization is not common in children. We suggest that the following investigations could be performed in children to aid in assessing the risk of PE. It should be noted none of these tests have been studied extensively in pediatrics for risk assignment.

Electrocardiogram

Electrocardiogram is fundamentally based on changes from cor pulmonale and subsequent right heart strain (2). This may show right axis deviation, right bundle branch block, sinus tachycardia, ST segment, and T wave abnormalities in adult patients (the classic S1Q3T3 pattern), but is not reliable or validated in pediatrics (32).

Echocardiogram

A 2D echocardiogram is an imaging modality that can examine both direct and indirect results of a PE. In adults, it allows for the ability to reasonably predict which patients are at risk for severe outcomes. These signs may include right ventricle dilatation, hypokinesis and abnormal motion of the interventricular septum, tricuspid regurgitation, and lack of collapse of inferior vena cava during inspiration. RV free-wall hypokinesis that does not affect the apical segment is highly specific, but not very sensitive (2, 33).

Biomarkers

Several biomarkers, such as cardiac troponin, brain-type natriuretic peptide, and heart type fatty acid-binding protein, have been shown in adults to increase the risk of adverse outcomes in PE and may be performed in children (18, 34, 35). The ranges of such biomarkers have not been established in children, and as such their clinical utility is uncertain.

Other Ancillary Tests

Other ancillary studies that are usually performed include complete blood count with differential, prothrombin time, activated partial thromboplastin time, and fibrinogen level; renal and liver function tests should be performed prior to initiating anticoagulant therapy to assess any risk of bleeding. In addition, if pharmacologic therapy is being considered, a plasminogen level may be measured as neonates and children may often be deficient and supplementation with plasma may be needed to obtain the necessary therapeutic effect. Furthermore, clinicians should examine extremities and all four limbs should have ultrasonography to evaluate for any associated DVTs (36). Chest radiography, while not helpful in the diagnosis of PE, is very helpful in the exclusion of other lung pathologies.

Thrombophilia Testing

The Subcommittee of Perinatal and Pediatric Thrombosis of the Scientific and standardization Committee of the International Society on thrombosis and Hemostasis recommend that all children with thrombosis be tested for thrombophilia (as described in **Table 1**). However, the role of thrombophilia in categorization of risk, management, and outcomes has not been elucidated yet for pediatric PE (37).

TREATMENT

Prompt recognition and diagnosis is of utmost importance to not only prevent progression and adverse sequelae of underlying PE but also to avoid unnecessary invasive treatment (38). Recommendations for management of the pediatric patients with PE have been extrapolated from adult data (2, 7, 39). Given the differences in pharmacokinetics and etiologies among children and adolescents compared to adults, however, management decisions should be specifically geared toward this particular population rather than simply based off of adult data (39).

There are no specific treatment algorithms for management of PE in children. Each institution should consider a treatment approach that works best for the individual setting. Some centers have developed pulmonary embolism response teams with involvement from multidisciplinary teams, such as hematology, emergency department, intensive care, and interventional cardiologists (31). Patients who present with signs and symptoms of high risk PE may benefit from either pharmacologic (**Table 2**) or mechanical thrombolysis. The goal of thrombolysis is to aim at a faster clot resolution, thus reducing right ventricular strain. Recombinant tissue plasminogen activator (rtPA; alteplase), streptokinase, or urokinase have been used for pharmacologic thrombolysis. Over the last several years, rtPA has been used more frequently due to its low immunogenicity, improved availability, *in vitro* clot lysis activity, and fibrin specificity (40). Thrombolysis may be delivered *via* a peripheral vein (systemic thrombolysis) or *via*

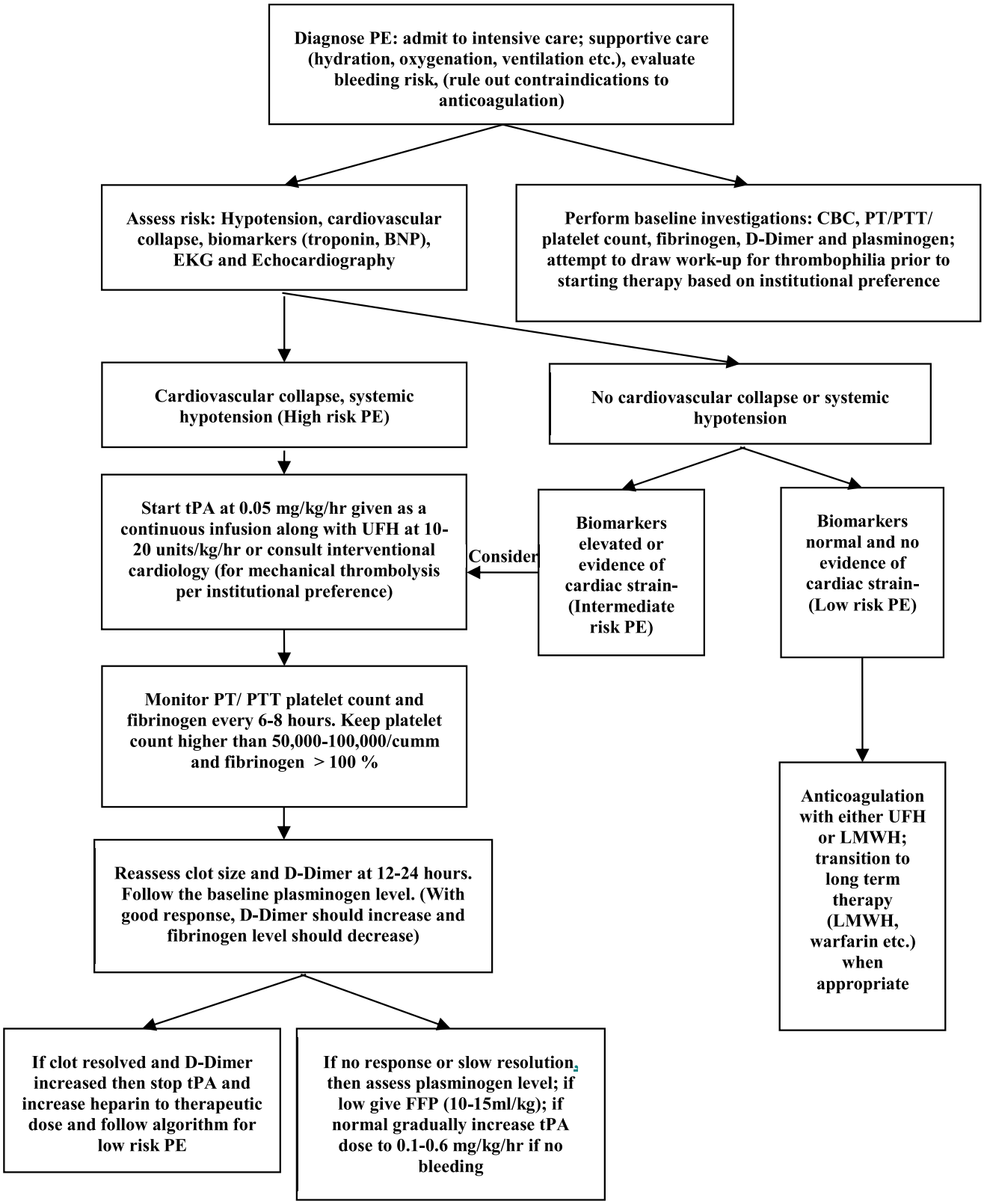

FIGURE 1 | Treatment algorithm for pulmonary embolism.

catheter-directed thrombolysis where-in a catheter is placed in close proximity to the clot. Although there are no specific preferences, in general, catheter-directed therapy is preferred if there is a higher perceived risk of bleeding. Furthermore, although there are ACCP guidelines concerning dosing, the optimal dose for rtPA for the management of pediatric PE has not been established. Currently, there are two dosing regimens with each presenting potential advantage. One regimen uses rtPA at a higher dose of 0.1–0.6 mg/kg/h for 6 h. While this may offer the advantage of improved clot resolution, there may be higher risk of bleeding. On the other hand, a low-dose regimen consisting of 0.03–0.06 mg/kg/h with a maximum dose of 2 mg/h has been shown to be efficacious with less risk of bleeding (41). We present a treatment algorithm (**Figure 1**) that we follow at our center. In our dosing guideline, we start thrombolysis at a low dose and then escalate to a higher dose if no response is seen. Mechanical thrombolysis and surgical thromboendarterectomy may be utilized for patients with high risk of bleeding or with contraindications to anticoagulation, if pharmacologic treatment has failed or if the patient presents with hemodynamic collapse.

Unfractionated heparin (UFH: 75 U/kg over 10 min intravenous followed by 20 U/kg/h for patients >1 year, 28 U/kg/h for <1 year of age) and low molecular weight heparin (LMWH: 1 mg/kg twice daily subcutaneously for patients >2 months of age, 1.5 mg/kg twice daily subcutaneously for patients <2 months of age) remain the most commonly used initial therapies for children with PE. If the patient is not clinically stable or has a higher risk of bleeding, UFH may be used as this is easily reversible and has a shorter half-life. Long-term treatment consists of either LMWH or warfarin. The duration of therapy in PE has not been defined and treatment duration has varied from 3 months to 1 year. Newer direct oral anticoagulants such as rivaroxaban, which directly inhibits factor Xa, have been studied in randomized controlled trials among adults for use in PE (42), but their safety and efficacy have yet to be established among the pediatric population.

FOLLOW-UP

It is important to continue to follow pediatric patients in the acute setting of PE to determine the immediate outcome (resolution, progression, and recurrence) and to monitor for potential long-term complications, such as pulmonary hypertension and chronic PE (43). The sequelae of PE among children, however, are not well studied (7). Hancock et al. conducted a mixed retrospective-prospective cohort study of patients less than 21 years of age with PE (44). They studied 58 patients (47 of who were prospectively followed). Echocardiography was obtained in the acute period in 24 patients assessing the presence of right heart dysfunction. Four patients had one parameter suggestive of acute right heart dysfunction, five had two parameters, and one had all three. EKGs were obtained in 32 patients in the acute setting in which 13 had ST/T segment changes, four showed the classic S1Q3T3 pattern and two had voltage consistent with right ventricular hypertrophy. During the first 6-month follow-up period, 11 patients underwent echocardiography of whom two had tricuspid velocity >3 m/s, three had septal flattening, and four had right ventricular dilation. An additional 15 patients had echocardiography after 1 year of whom only 13% had septal flattening and right ventricular dilation. These results indicate that among the pediatric population with acute PE, acute cardiac dysfunction is relatively common but not in the chronic setting (44). Additional findings noted that five patients developed recurrent, symptomatic PE and there was a non-resolution of 18% among patients who underwent repeat imaging 6 months after the acute event.

NEW/EMERGING CONCEPTS

For unstable patients, catheter-directed modalities are generating more interest, though pediatric data regarding the use and feasibility of these modalities are limited. Ultrasound-assisted thrombolysis (USAT) uses catheter-directed high frequency ultrasound to assist in penetration of a thrombolytic agent into the embolus. Two large adult studies have shown no difference in mortality or major bleeding between groups getting USAT with a fibrinolytic agent versus conventional anticoagulation (45, 46). Rheolytic embolectomy (the most common type being the AngioJet) injects pressurized saline into the embolus while aspirating macerated thrombus through the catheter port. Early adult data show promising results for patients with PE (47, 48). A major disadvantage of this procedure is that mandatory venotomy is required for insertion, which increases the bleeding risk. Rotational embolectomy uses a rotating device at the catheter tip that fragments the thrombus, in conjunction with continuous aspiration. In one adult study, 89% of patients with shock due to PE were stabilized (49). Suction embolectomy and thrombus fragmentation with rotation of a pigtail catheter or use of a balloon angioplasty catheter are also treatment modalities that are occasionally used in conjunction with USAT, rheolytic embolectomy, and rotational embolectomy. Perhaps the largest study in the pediatric population, studying 21 aspiration and rheolytic thrombectomies (5 of the pulmonary vasculature) at Texas Children's Hospital, showed that such interventions can be performed safely even in critically ill children with life-threatening thrombosis (50).

FUTURE RESEARCH

Currently, there is an ongoing clinical trial to determine the optimal duration of treatment (6 weeks versus 3 months) for children with provoked DVT (51). This trial, however, does not allow enrollment of patients with PE. Prospective trials specifically addressing risk categorization and optimal treatment of pediatric PE are desperately needed.

CONCLUSION

Pulmonary embolism is a rare, but potentially fatal, condition that often goes unrecognized among the pediatric population. It is critical to maintain a high index of suspicion of PE particularly among patients at greatest risk, including patients with a CVL, congenital heart disease or other conditions known to

predispose to PE (obesity, hormonal supplementation, etc.). Diagnostic prediction models for the diagnosis of PE, such as the Wells criteria and Geneva score, have been validated among the adult population; however, there are no similar models for use among children and adolescents that are greatly needed. CT angiography is the primary modality utilized for diagnosis of PE in this age group. The mainstay of treatment remains UFH, LMWH, or warfarin for these patients, and trials are ongoing to determine the utility of newer oral anticoagulants as potential alternatives. It is critical that the field of pediatric hematology continues to focus research on patients with acute and chronic VTE not only to improve the knowledge and understanding of this disease process but to provide improved, evidenced-based care for these patients.

AUTHOR CONTRIBUTIONS

AZ and KH wrote the manuscript and contributed equally to the body of the text. MR revised the manuscript and generated key tables and figures. All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Venous Thromboembolism in Children with Cancer and Blood Disorders

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Venous thromboembolism (VTE) in children is multifactorial and most often related to a combination of inherited and acquired thrombophilias. Children with cancer and blood disorders are often at risk for VTE due to disease-related factors such as inflammation and abnormal blood flow and treatment-related factors such as central venous catheters and surgery. We will review risk factors for VTE in children with leukemia, lymphoma, and solid tumors. We will also review risk factors for VTE in children with blood disorders with specific focus on sickle cell anemia and hemophilia. We will present the available evidence and clinical guidelines for prevention and treatment of VTE in these populations.

Keywords: venous thromboembolism, cancer, blood disorders, pediatrics, thromboprophylaxis

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VENOUS THROMBOEMBOLISM IN CHILDREN WITH CANCER

Venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) result in significant morbidity and mortality in individuals with cancer. VTE is a leading cause of death in adults with cancer (1). As care for critically ill children improves, the incidence of VTE in children is increasing (2). The general incidence of VTE in children ranges from 0.7 to 1.4 VTE/100,000 children and 53 VTE/100,000 hospital admissions (3–5). Children with cancer make up one of the largest subsets of patients who experience VTE (2). A study using the 1994–2009 Nationwide Inpatient Samples identified cancer as one of the primary risk factors for pediatric VTE-related hospital admissions (6). Other identified risk factors, central venous catheter (CVC) use, mechanical ventilation, and hospitalization of >5 days are common in this population.

VTE occurs in 2.1–16% of children with cancer (7–10). Rates vary based on the diagnostic imaging modality and whether VTE is symptomatic or asymptomatic. The rate is higher when patients who were screened for asymptomatic VTE are included (10, 11). Walker et al. conducted a population-based cohort study in the United Kingdom to compare rates of VTE between children with and without cancer. In this study, the absolute rate of VTE in children with cancer was 1.52 per 1,000 person-years (95% CI = 0.57–4.06) versus 0.06 per 1,000 person-years (95% CI = 0.02–0.15) in controls without cancer [hazard ratio of 28.3 (95% CI = 7.0–114.5)] (12).

The occurrence of VTE varies by cancer type (12). In a population-based cohort study utilizing national databases in the UK, the rate of VTE per 1,000 person-years in pediatric controls was 0.06 (95% CI 0.02–0.15) compared to 1.5 (95% CI 0.6–4.1) in all pediatric cancers, 0.9 (95% CI 0.1–6.1) in leukemia/lymphoma, 8.1 (95% CI 2.0–33.0) in soft tissue sarcoma/bone tumors, and 4.0 (95% CI 0.6–29.0) in other sites. In this report, there was no reported VTE in children with brain tumors. Much of the literature in children with cancer focuses on patients with acute lymphoblastic leukemia (ALL), the most common pediatric malignancy. A meta-analysis of children with leukemia reported

VTE in 5.2% of children with ALL, but reported rates range from 1 to 36% (13–15). VTE occurs in 7–16% of patients with soft tissue sarcomas (16, 17). Interestingly, though thrombosis is often seen in adults with brain tumors, the incidence of thrombosis in children with brain tumors is quite low and ranges from <1 to 2.8% (7, 18, 19).

The etiology of VTE in children with cancer is multifactorial and includes genetic predisposition (thrombophilia), disease-related factors, and treatment-related factors including use of CVC, surgery, and chemotherapy. A Canadian multicenter case–control study of children with cancer identified age (≤2 and >10 years), blood group (non-O), and use of L-asparaginase as independent risk factors for DVT occurrence (20).

Cancer may be considered a hypercoagulable state. Albayrak et al. found activated coagulation and reduced fibrinolysis in children with ALL prior to chemotherapy (21). Giordano et al. identified thrombin generation at ALL diagnosis (22). The pathophysiology of this hypercoagulable state is related to secretion of cytokines and clotting factors by cancer cells (23). Pediatric tumors with mass effect impair blood flow and increase risk of VTE. In children with lymphoma, the presence of a mediastinal mass, which compresses upper extremity veins, increases the risk of thrombosis (24). Renal tumors with vascular invasion are also associated with VTE.

The majority of children with cancer have CVC placed for administration of chemotherapy and other supportive care. CVC is the most common risk factor for VTE in children with cancer. Reported rates of symptomatic catheter-related VTE range from 2.6 to 36.7%, and rates of asymptomatic catheter-related VTE range from 5.9 to 43% (25–27).

Certain aspects of cancer treatment increase the risk of thrombosis. Giordano et al. prospectively monitored changes in the coagulation parameters of children with ALL and showed that treatment for ALL altered the quantity and activity of numerous hemostatic proteins (22).

L-Asparaginase, which is used for treatment of ALL, is a well described risk factor for VTE. L-Asparaginase has widespread effects on coagulation including reduction in antithrombin. Steroids (particularly prednisone) increase factor VIII von Willebrand factor, which contributes to prothrombotic risk (23, 28, 29).

Additional prothrombotic risk factors include catheter-related blood stream and other infections in the immunocompromised patients as well as immobility during hospitalization, particularly in the post-operative period.

VTE results in serious consequences, including death. In a meta-analysis of children with ALL who developed VTE, about half of events occurred in the central nervous system (CNS). Fifteen to twenty percent of CNS thrombosis results in long-term neurologic sequelae (30–32). The Nordic Society of Paediatric Haematology and Oncology followed 20 patients with ALL and cerebral sinus venous thrombosis (CSVT), two of whom had deaths attributed to CSVT (33). Post-thrombotic syndrome (PTS), a chronic complication of VTE associated with chronic leg swelling, pain, and sometimes skin changes including ulceration, complicates both symptomatic and asymptomatic VTE (34). Polen et al. conducted a prospective cohort study of children with a history of cancer after CVC removal. PTS occurred in 30.5–34% of patients depending on the method of diagnosis. A history of CVC occlusion, DVT, or multiple CVC placements was associated with PTS (35).

Treatment and Prevention of Venous Thromboembolism in Children with Cancer

There are no specific guidelines for treatment of VTE in children with cancer. The anticoagulants most commonly used in children are warfarin and heparins (36). There are ongoing clinical trials of anticoagulants in pediatric oncology patients, but no results have been published. Clinicians must consider the increased risk of bleeding in oncology patients who have thrombocytopenia and either withhold anticoagulation at low platelet counts or transfuse platelets at a lower threshold.

Thromboprophylaxis guidelines are well established for adults with cancer (37, 38). No such guidelines exist for children, even for those without cancer. There are limited data on prophylactic strategies of warfarin, low-molecular-weight heparin (LMWH), and antithrombin replacement in pediatric oncology patients with ALL (26, 39–46). None of these studies resulted in evidence-based strategies to prevent thrombosis. Nowak-Göttl et al. conducted an uncontrolled study of prophylaxis with LMWH in children with sarcomas; none developed VTE (47).

Several investigators have developed risk prediction models. Mitchell et al. published a validated, predictive model for the development of VTE in patients with ALL, which may be adapted to local patient population and practice to prevent VTE (43, 48). Bell et al. also published an approach to risk assessment and prophylaxis in this population (49). The Italian Association of Pediatric Hematology and Oncology made recommendations specifically for prolonged use of CVC in children with cancer and blood disorders. They recommend insertion of the CVC on the right side of the upper venous system and also the placing of the tip of the CVC at the right atrial–superior vena cava junction (50). These recommendations are based on studies showing higher rates of thrombosis when CVCs were placed on the left side and not placed at the right atrial–superior vena cava junction (51, 52).

Summary

Children with cancer are at risk for developing VTE secondary to disease- and treatment-related factors and other inherited and acquired conditions. However, there is still much to be learned regarding risk factors, prevention, and treatment of VTE in this population.

VTE IN CHILDREN WITH BLOOD DISORDERS

VTE has been reported in children with acquired and inherited blood disorders. VTE occurs secondary to a combination of (1) underlying disease pathophysiology; (2) complications of disease; and (3) treatment of disease including medication, CVC placement, and surgery. See **Table 1**.

TABLE 1 | Risk factors for venous thromboembolism in children with cancer and blood disorders.

	Cancer[a]	Sickle cell anemia[a]	Hemophilia
Central venous catheter	Chemotherapy Supportive Care	Chronic blood transfusions Erythrocytapheresis	Prophylaxis Immune tolerance induction
Surgery	Surgical management of cancer	Splenectomy[b] Cholecystectomy Orthopedic procedures	Orthopedic procedures
Immobility due to pain	Cancer and treatment-related pain	Vaso-occlusive pain crisis Avascular necrosis	Joint or muscle hemarthrosis Chronic arthropathy
Infection	Sepsis and other invasive infection secondary to immunocompromised state	Sepsis secondary to functional and/or surgical asplenia Osteomyelitis Acute chest syndrome	Sepsis
Medication	Asparaginase Corticosteroids Erythropoietin	Erythropoietin	Factor replacement Bypassing agents

[a]*Underlying disorder is associated with hypercoaguability.*
[b]*Postsplenectomy state is associated with increased risk of VTE.*

A number of blood disorders are associated with inherent hypercoagulable states including [sickle cell anemia (SCA), see below]; vascular malformations (disseminated intravascular coagulation); hemophagocytic lymphohistiocytosis (hyper-inflammatory state); immune thrombocytopenic purpura (ITP); and autoimmune hemolytic anemia (AIHA) (53). Management of blood disorders with splenectomy is noteworthy, because the postsplenectomy state is associated with increased risk for VTE (54, 55). Splenectomy is indicated in children with SCA who suffer recurrent splenic sequestration and hypersplenism. Children with thalassemia may undergo splenectomy to increase red cell survival and decrease transfusion requirements. Splenectomy is an alternative to medical management in some cases of ITP, AIHA, and hereditary spherocytosis.

The rest of this section will focus on VTE in SCA and hemophilia.

VTE in SCA

Sickle cell anemia is a hemoglobinopathy characterized by the presence of hemoglobin S. Clinical manifestations result from red cell hemolysis and vaso-occlusion. Acute complications include pain, acute chest syndrome (ACS), stroke, priapism, and splenic sequestration. Chronic complications include pulmonary hypertension, splenic dysfunction, and avascular necrosis (AVN).

Data are sparse in regards to the rates of VTE in children with SCA. Primary data include case reports of VTE (56–59), case series of catheter-related thrombosis (see below), and data within larger adolescent and adult cohort studies. In the Cooperative Study of Sickle Cell Disease, including 1,523 patients aged ≥15 years, the rate of first VTE was 5.2 per 1,000 person-years; including a PE rate of 3.6 per 1,000 person-years and isolated DVT rate of 1.6 per 1,000 person-years. Then, 11.3% had a least one VTE by age 40 years. Rates were highest in association with SS and $S\beta^0$ thalassemia, and VTE was associated with higher risk of death.

Rates of VTE are expected to be higher than the general population, because, in addition to the baseline prothrombotic state, children and adolescents with SCA have other disease-related risk factors for VTE. Of note, VTE occurs starting at a younger age in adults with SCA compared to African-American controls; in a study of hospitalized patients with SCA, the mean age of patients with PE was 28 years compared to 57 years in controls and the mean age of patients with DVT was 31 years in patients with SCA compared to 54 years in controls (60).

The coagulation system is activated in SCA and SCA may be considered as a hypercoagulable state with higher levels of platelet activation, thrombin generation, and inflammation (61–66). Anticoagulants and antiplatelet agents are being studied as novel therapeutic agents for prevention complications in SCA (67).

The most common risk factor for VTE in children with SCA is presence of a CVC. CVC may be placed for short- and long-term venous access (68–71). A temporary CVC may be placed acutely during hospitalization for individuals with poor venous access, who are acutely ill and require intensive care, or in individuals with poor venous access requiring prolonged duration of intravenous therapy. Apheresis catheters are placed to facilitate exchange transfusion in the setting of stroke or ACS. Single or double lumen CVC is inserted to facilitate chronic red cell transfusions or exchange transfusion for primary and secondary stroke prevention (72). Jeng et al. reported a rate of catheter-related thrombosis of 0.99 per 1,000 catheter days in patients aged 1.4–30 years; 33% of the reported patients had catheter-related thrombosis (69). Shah et al. reported a rate of catheter-related thrombosis of 0.49 per 1,000 catheter days in patients aged 1–59 years; 41% of the reported patients had catheter-related thrombosis (68).

Other acquired prothrombotic risk factors in SCA include obesity, immobility, infection, and splenectomy. Although growth failure is a concern in children with SCA, rates of obesity, a known risk factor for VTE, are rising in children with SCA (73). Individuals with SCA may have chronic or acute immobility. Chronic immobility is related to chronic pain including pain from AVN. Acute immobility occurs during hospitalization for vaso-occlusive pain and other sickle cell-related complications and at the time of surgery for surgical procedures including abdominal (i.e., splenectomy, cholecystectomy) and orthopedic procedures (i.e., core decompression). Children and adolescents are at risk for invasive infections due to functional asplenia. Infectious complications include bacterial sepsis, ACS, and osteomyelitis. Other risk factors reported in adults with SCD SC and Sβ+ include higher hemoglobin and history or surgical splenectomy (74).

Clinicians must include VTE on the differential diagnosis of extremity and limb pain. If DVT occurs in the setting of vaso-occlusive crisis, diagnosis of DVT may be delayed if pain is attributed to vaso-occlusive crisis or other sickle cell-related complication. Chest pain occurring in hospitalized patients with SCA is most often attributed to vaso-occlusive crisis or ACS. PE must also be suspected in patients with significant chest pain and hypoxia. If PE is diagnosed, then extremity ultrasonography should be done to determine if thrombosis is truly embolic

or *in situ*. Those with PE may be at higher risk for pulmonary hypertension (75).

D-Dimer is increased at baseline in SCA; therefore, D-dimer has lower prognostic significance in the diagnosis of VTE in SCA.

Treatment and Prevention of VTE in Children with SCA

There are no specific guidelines for treatment of VTE in patients with SCA. Guidelines for prevention of VTE in hospitalized pediatric patients are still under development. Even in the adult population, there are no disease specific recommendations for SCA. Clinicians who take care of children and adolescents with SCA should evaluate patients for acquired prothrombotic risk factors and consider thromboprophylaxis if multiple risk factors are present.

VTE in Children with Hemophilia

Although children with hemophilia are primarily at risk for bleeding and should be at lower risk of VTE due to clotting factor deficiency, thrombotic complications do occur. Thrombotic complications in this population are most often attributed to CVC, clotting factor replacement, and disease-related complications.

Occurrence of VTE

Data are sparse on rates of thrombosis in children with hemophilia. Primary data include case reports and case series of children with catheter-related thrombosis.

As with SCA, CVC is the most common risk factor for VTE in children hemophilia. CVC is most often placed in children with hemophilia who require reliable venous access for prophylaxis, prophylactic clotting factor replacement administered one to four times per week, or immune tolerance induction, high-dose clotting factor administration up to 7 days per week for inhibitor eradication (76). Although Medeiros et al. reported a low rate of catheter-related thrombosis in children with hemophilia (77), subsequent publications document asymptomatic and symptomatic catheter-related thrombosis in patients with hemophilia (78–81). Risk may increase with duration of catheter presence (81). Even asymptomatic VTE are important to recognize given the risk and morbidity of PTS (79, 80). Consensus recommendations for use of CVC in hemophilia include the following: use of the smallest possible catheter diameter, position the catheter tip in the lower third of the superior vena cava, evaluate for catheter-related thrombosis after 2–4 years, and transition to peripheral access as soon as possible if thrombosis is detected (82). In general, due to the risk of catheter-related thrombosis, CVC should be avoided when possible and removed as soon as peripheral venous access is reliable for factor administration.

Other acquired prothrombotic risk factors include obesity, immobility, orthopedic surgery, infection, and high doses of clotting factor replacement. Rates of overweight and obesity are high in hemophilia (83, 84). This may be related to restricted activities. Children with hemophilia may suffer acute immobility due to joint and muscle bleeds and less commonly chronic immobility due to hemophilic arthropathy. VTE in persons with hemophilia ≤18 years has been described in the setting of major orthopedic surgery (85, 86). Orthopedic procedures are less common in children with hemophilia than in adults. Nonetheless, if a pediatric patient with hemophilia undergoes a major orthopedic procedure then patient should be fully assessed for any additional risk factors for thrombosis such as obesity and preventive measures may be considered (87, 88). Children with hemophilia are not inherently immunocompromised but may have CVC-related infection or infection in the setting of immunomodulatory therapy for inhibitors.

Patients with hemophilia and inhibitors often require high and frequent doses of bypassing agents for treatment of bleeding and factor replacement for ITI. Silvey et al. described cases of PE in young children with hemophilia A and high-titer inhibitors (89). Girolami et al. also described a higher frequency of thrombosis in inhibitor patients (90).

The most common etiologies of swelling in the lower or upper extremities in children with hemophilia are hemarthrosis, intramuscular bleed, and soft tissue bleeds. Therefore, clinicians likely have a lower index of suspicion for VTE as a cause of swelling and pain in the extremities, and the diagnosis of VTE in this patient population may be missed or delayed. Despite the bleeding phenotype of hemophilia, clinicians should maintain an index of suspicion for VTE in children with inherited bleeding disorders who have multiple prothrombotic risk factors.

Treatment and Prevention of VTE in Children with Hemophilia

Martin and Key recently published an approach to treating patients with inherited bleeding disorders who need anticoagulant therapy (91). The authors point out that there are no standardized guidelines. When deciding whether or not to initiate anticoagulation, the patient's bleeding phenotype must be balanced against the risk of developing or not treating thrombosis. In some cases, prophylactic clotting factor to increase factor levels >30% and decrease risk of bleeding may be required to allow for safe anticoagulation. Short-acting and reversible therapeutic agents are favored due to higher risk of bleeding. The intensity and duration of therapy must be carefully considered to minimize bleeding outcomes while achieving desired anticoagulant outcome.

Summary

Children with blood disorders are at risk for VTE secondary due to disease-related factors, disease complications, and disease management. Care should be taken to target modifiable risk factors, to educate patients about signs and symptoms of VTE, and to consider thromboprophylaxis in the setting of multiple prothrombotic risk factors.

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MINI REVIEW
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Cerebral Sinovenous Thrombosis

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Cerebral sinovenous thrombosis (CSVT) is a rare but serious cerebrovascular disorder affecting children from the newborn period through childhood and adolescence. The incidence is estimated at 0.6/100,000/year, with 30–50% occurring in newborns. Causes are diverse and are highly age dependent. Acute systemic illness is the dominant risk factor among newborns. In childhood CSVT, acute infections of the head and neck such as mastoiditis are most common, followed by chronic underlying diseases such as nephrotic syndrome, cancer, and inflammatory bowel disease. Signs and symptoms are also age related. Seizures and altered mental status are the commonest manifestations in newborns. Headache, vomiting, and lethargy, sometimes with 6th nerve palsy, are the most common symptoms in children and adolescents. Recent multicenter cohort studies from North America and Europe have provided updated information on risk factors, clinical presentations, treatment practices, and outcomes. While systemic anticoagulation is the most common specific treatment used, there are wide variations and many uncertainties even among experts concerning best practice. The treatment dilemma is especially pronounced for neonatal CSVT. This is due in part to the higher prevalence of intracranial hemorrhage among newborns on the one hand, and the clear evidence that newborns suffer greater long-term neurologic morbidity on the other hand. With the advent of widespread availability and acceptance of acute endovascular therapy for arterial ischemic stroke, there is renewed interest in this therapy for children with CSVT. Limited published evidence exists regarding the benefits and risks of these invasive therapies. Therefore, the authors of current guidelines advise reserving this therapy for children with progressive and severe disease who have failed optimal medical management. As research focused on childhood cerebrovascular disease continues to grow rapidly, the future prospects for improving knowledge about this disorder should be good.

Keywords: cerebrovascular disorders, stroke, thrombosis, neonatal, childhood

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DEFINITIONS, INCIDENCE, AND SPECTRUM OF DISEASE

Cerebral sinovenous thrombosis (CSVT) encompasses a spectrum of disorders involving thrombosis of the cerebral venous system. The incidence in Europe and North America is estimated at 0.6 per 100,000 per year in childhood, with a male predominance (60–70%), and neonates accounting for 30–50% of cases (1, 2). The cerebral venous system is composed of a network of cortical, medullary, and deep veins which drain into dural venous sinuses. These comprise the superficial dural sinuses (sagittal, transverse, and sigmoid) and the deep venous system (straight sinus, vein of Galen) (see **Figure 1**). Thrombosis in the cerebral venous system impedes venous outflow, resulting in increased central venous pressure, which in turn causes intracranial hypertension. In some cases, this leads to cerebral ischemia, which may evolve to infarction, often hemorrhagic. In the most severe cases, diffuse cerebral edema and widespread infarction and hemorrhage may result in permanent

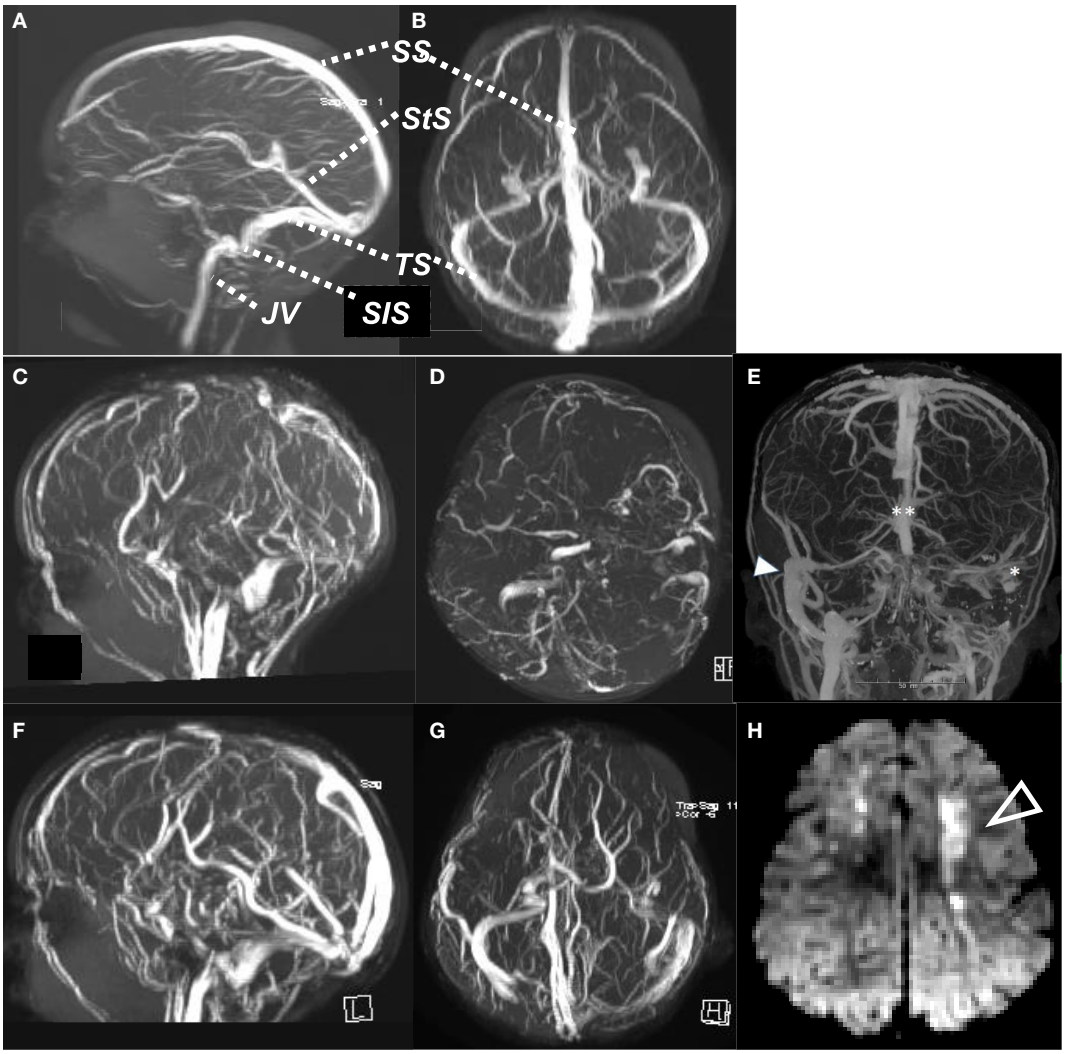

FIGURE 1 | Normal MR venogram, sagittal view **(A)**, axial view **(B)**. Case of cerebral sinovenous thrombosis, acute MR venogram sagittal **(C)** and axial **(D)**, showing absent flow signal in SS, both TS and StS, with ischemic change (arrow) in cortical white matter on DWI **(H)**. Computed tomography venogram **(E)** of child with mastoiditis and occlusive thrombus of left SiS and TS (*) and distal SS (**), compared to patent right SiS and TS (arrow). MR venogram 6 months later **(F,G)**, with recanalization of SS, StS, and TS. SS, sagittal sinus; StS, straight sinus; TS, transverse sinus; SiS, sigmoid sinus; JV, jugular vein.

neurologic disability, or herniation and death. Risk factors are diverse and are related to age, as well as the presence of acute or chronic illnesses, and thrombophilias (**Table 1**). The long-term outcome of CSVT in children is variable and depends on the age of incident disease, comorbid diseases, and presence of acute complications (**Table 2**). Neonates in general have a greater risk of poor outcomes, including motor and cognitive impairments and, notably, epilepsy. Children with CSVT mostly do well and make a full recovery. Recurrence rates are low (<10%).

CAUSES AND RISK FACTORS

Causes and risk factors for CSVT are age dependent and highly variable (3, 4, 8, 9). They can best be understood in the context of Virchow's triad: slowing or stasis of blood flow, injury or disruption of the vessel wall, and perturbation of the components of blood affecting clot formation and lysis. Frequently there are multiple coexisting inciting conditions and underlying risk factors. Among newborns, acute systemic illness, infection, and fluid/electrolyte disturbances are most common. Among previously healthy children, CSVT most often occurs in the setting of head/neck infections, acute illness with dehydration and iron deficiency anemia. Chronic illnesses that predispose children to CSVT include inflammatory bowel disease, cancer, autoimmune disorders, and chronic kidney disease, among others. Recently published multicenter cohort studies have described the most common risk factors and underlying conditions as shown in **Table 1**. Consistent findings across multiple cohort studies are that neonates have distinct risk factor profiles compared to children. Among neonates, exposure to perinatal stress (hypoxia/ischemia, difficult birth), and acute systemic illness such as sepsis, pneumonia, and respiratory distress syndrome are the leading

TABLE 1 | Risk factors for cerebral sinovenous thrombosis (CSVT) in pediatric cohort studies.

Risk factor or inciting illness	Prevalence of risk factor (%)[a]						
	Ichord et al. (3) (IPSS)	Jordan et al. (4) (IPSS)	Grunt et al. (1) (Swiss)		Moharir et al. (5, 6) (Canadian)		Berfelo et al. (7) (Netherlands)
	N = 170 children	*N* = 84 neonates	*N* = 42 children	*N* = 21 neonates	*N* = 79 children	*N* = 83 neonates	*N* = 52 neonates
Acute systemic illness[b]	46	63	–	80	28	37	23
Acute head/neck infection or meningitis[c]	54	–	63	5	47	34	–
Prothrombotic state[d]	20	10	42	42	84/25[h]	67/21[h]	24
Hematologic disorder[e]	10	–	2	–	n/r[i]	n/r	–
Cancer	12	–	14	–	n/r	n/r	–
Immunologic disease[f]	4	–	14	–	n/r	n/r	–
Cardiac disease	2	13	9	–	n/r	n/r	2
Other chronic disease[g]	5	–	5	–	53[i]	18[i]	–

IPSS, International Pediatric Stroke Study.
[a]Risk factors, note that many patients have multiple risk factors.
[b]Acute systemic illness—sepsis, respiratory failure, hypoxia/ischemia, gastroenteritis, dehydration.
[c]Acute head/neck infection—mastoiditis, sinusitis.
[d]Prothrombotic state—deficiencies in protein C, protein S, antithrombin III, factor V Leiden or prothrombin gene mutation, homocysteine elevation, lipoprotein a elevation, anticardiolipin antibodies, lupus anticoagulant.
[e]Hematologic disorder—anemia, hemoglobinopathies.
[f]Immunologic disease—lupus, Behcet's disease.
[g]Other chronic disease—diabetes, nephrotic syndrome, inflammatory bowel disease.
[h]At diagnosis/persistent on f/u testing.
[i]n/r, not specifically reported, pooled into "chronic systemic disease."

TABLE 2 | Anticoagulation treatment practices and outcomes.

Study	Population studied	*N*, median age, gender	AC Rx (%)	Outcome (%)		
				Mortality	Adverse outcomes	Epilepsy
Sébire et al. (8)	Europe 1993–2002	42 children, 5.7 years, 64% male	42	12	33	7
Mallick et al. (2)	United Kingdom 1997–2005	21 children, 7.1 years, 47% male	100, tPA 4/21	9	48	n/a
Mohariret al. (5)	Canada 1992–2005	83 neonates, 79 children, 5.5 years, 66% male	Neonates 35, children 71	Neonates 6, children 0	Neonates 59, children 37	n/a
Grunt et al. (1)	Switzerland 2000–2008	21 neonates, 67% male, 44 children, 8.7 years, 68% male	Neonates 33, children 90	9[a]	Neonates 38, children 4	Neonates 38, children 0
Berfelo et al. (7)	Netherlands 1999–2009	52 neonates, 75% male	42	20	55	n/a
Jordan et al. (4)	IPSS 2003–2007	84 neonates, 74% male	52	2	46[b]	n/a
Ichord et al. (3)	IPSS 2003–2007	170 children, 7.2 years, 60% male	83	4	52[b]	n/a

IPSS, International Pediatric Stroke Study; AC Rx, anticoagulation treatment; tPA, systemic thrombolysis.
[a]Deaths not directly related to CSVT.
[b]Abnormal neurologic exam at hospital discharge; long-term outcome unknown.

predisposing and comorbid conditions. In childhood, previously healthy children develop CSVT mainly in the setting of acute treatable infections, in particular head and neck infections such as mastoiditis and sinusitis. Among children with chronic disease, certain diseases are particularly associated with a risk of CSVT due to disturbed regulation of coagulation or systemic circulation. These include complex congenital heart disease, inflammatory bowel disease, Behcet's syndrome, nephrotic syndrome, and leukemia, especially during treatment with L-asparaginase.

Abnormal levels of prothrombotic factors are common in neonates and children. Some abnormalities are inherited, while others are acquired and may be transient. There is controversy as to whether some of these may be epiphenomena, coincidental vs causal in nature. Large scale case–control studies in adults with CSVT provide good evidence that certain prothrombotic risk factors do occur with a prevalence estimated at 30–35%, and indeed contribute to the causation of CSVT, often in combination with other inciting or comorbid diseases (10, 11). The prothrombotic factors most studied and shown to increase the risk of CSVT include deficiencies of protein C, protein S, and antithrombin III; mutations in the factor V Leiden and prothrombin genes; elevated blood levels of homocysteine; elevated anticardiolipin antibodies and lupus anticoagulant; elevated levels of lipoprotein a. Pediatric cohort studies and case–control studies report somewhat higher prevalence rates of prothrombotic factors than in adults, ranging from 25 to 60% and confirm associations with similar risk factors as in adults (12, 13). The Canadian cohort study evaluated the prevalence of prothrombotic factors acutely and again at follow-up, showing that many of the abnormalities in factor levels detected acutely normalized on follow-up testing

(5). Interpretation of such abnormalities is especially complex among newborns, where the levels of endogenous fibrinolytic factors such as protein C and S are normally low based on age, or may be decreased secondarily by the acute illness. These observations mean that results of cohort studies must be interpreted with caution and can only be understood in the context of age-specific norms, the state of the child at the time of testing, and results of follow-up testing (14).

CLINICAL SIGNS AND SYMPTOMS

Clinical signs and symptoms of CSVT are highly variable depending on age and underlying acute or chronic illness (3, 7–9). In many cases, the diagnosis may be challenging because symptoms are non-specific and overlap with symptoms of the underlying illness. Neonates present with depressed mental status and seizures. Children with CSVT typically have a triad of symptoms that include depressed mental status, headache, and vomiting, which evolve in an unremitting and progressive manner over a period of days. Mental status changes are variable, and may involve only irritability and drowsiness, or may progress to stupor and coma. Seizures are common, especially in neonates and in children with depressed mental status, and may require video EEG monitoring in order to fully characterize seizure burden and guide anticonvulsant therapy. Physical exam findings may be limited to alterations in mental status, or may include signs of intracranial hypertension such as papilledema and sixth nerve palsy, or a bulging fontanelle in the newborn. Additional signs and symptoms will reflect the underlying provoking illness, such as meningismus in the case of meningitis, or mastoid region tenderness and swelling in the case of mastoiditis. Cavernous sinus thrombosis presents as a distinct clinical syndrome, classically involving a combination of proptosis and chemosis of the involved eye, oculomotor palsies involving any combination of cranial nerves 3, 4, and 6, and sensory loss of the first division of the trigeminal nerve. Cavernous sinus thrombosis typically develops in the setting of infections involving the maxillary and ethmoid sinuses, or as an extension of mastoiditis, and has unique imaging requirements to make the diagnosis (see discussion of imaging in the Section "Diagnostic Approach: Update on Imaging Options and Best Practices"). Children with CSVT whose course is complicated by venous infarction or hemorrhage typically develop seizures and localizing deficits on examination such as hemiparesis, corresponding to the site of the infarction or hemorrhage. In the most severe cases, venous infarction with or without hemorrhage, combined with venous outflow obstruction, may lead to malignant intracranial hypertension, herniation, and death. In children who survive, uncontrolled intracranial hypertension and papilledema may progress to vision loss.

DIAGNOSTIC APPROACH: UPDATE ON IMAGING OPTIONS AND BEST PRACTICES

Timely diagnosis and treatment are critically important for optimizing outcome. As in arterial ischemic stroke, "time is brain" should be the guiding principle in managing CSVT. This begins with raising awareness of the clinical signs and symptoms, particularly among front line providers, for children who are at greatest risk—neonates, children with acute head/neck infections, and children with those chronic diseases carrying an increased risk of thromboembolism. These high-risk chronic diseases include those with congenital heart disease, nephrotic syndrome, immunologic disorders, anemia, and leukemia. The triad of symptoms—progressive unremitting headache, altered mental status, and vomiting—should prompt consideration of a diagnosis of CSVT, and to neuroimaging evaluation specifically targeting this condition. Neurologic consultation and direct dialog with radiologists are important strategies to determine the best modality and timing of imaging so as to guide treatment decisions in a timely way.

A variety of imaging modalities can be used. Magnetic resonance imaging (MRI) and MR venography offer the most detailed and sensitive means to assess the clot burden and extent of parenchymal injury. Greater availability of MRI, and improved quality of imaging, particularly with higher strength magnets, means that non-invasive imaging has largely replaced the catheter angiography for the diagnosis of CSVT. Computed tomography (CT) and CT venography provide generally high sensitivity for identifying thrombosis, but are less specific and less sensitive for characterizing brain injury. For example, Roland et al. found that non-enhanced CT has a 73% sensitivity for correctly identifying CSVT, with a very low rate of false positives (15). CT offers the advantage of greater accessibility and speed of imaging, but involves exposure to ionizing radiation and contrast, which is of particular concern in the pediatric population. MRI often is less readily available and requires more support from anesthesia/critical care to manage sedation. Radiologic confirmation of a diagnosis of cavernous sinus thrombosis has distinct requirements. It is best evaluated with contrast-enhanced brain MRI and will be missed by non-enhanced CT and by non-enhanced MRI and conventional MR venography (16).

Specific choices for imaging in any given case often depend on ease of access, time sensitivity for starting treatment, and the range of treatment decisions to be made. For example, a child with acute infectious mastoiditis who has intact mental status and only complains of headache will have treatment decisions involving possible surgical interventions that take priority over starting anticoagulation (AC). In such a case, obtaining the most detailed anatomical information about the brain and the parameningeal structures is most important for planning both the surgical and the antithrombotic treatment. MRI with and without contrast, and MRV, are most suitable in such a case. Contrasting this scenario is that of the child with inflammatory bowel disease who develops rapid and severe declining mental status and focal seizures during a disease flare. In cases like this, where time is of the essence, and sedation for lengthy MRI examination may proves practically challenging, then CT with CT venogram can provide the necessary data to confirm the diagnosis and to make rapid treatment decisions about antithrombotic therapy.

TREATMENT: UPDATES ON TREATMENT GUIDELINES AND CURRENT PRACTICES

There have been no clinical trials evaluating the risks and benefits of treatments for CSVT in children. Published treatment guidelines for children have largely been extrapolated from data obtained from adult studies (17–19). Treatment guidelines for adults recommend the following approach:

(1) Evaluation and treatment of patients with CSVT in facilities with specialized cerebrovascular expertise is appropriate and may be beneficial.
(2) Treatment with AC is safe and may be beneficial for reducing mortality and long-term morbidity, even in the presence of intracranial hemorrhage (ICH).
(3) There is insufficient evidence to show whether heparin or low molecular weight heparin (LMWH) is superior.
(4) The use of fibrinolytic therapy or endovascular therapy may be life-saving in critically ill patients experiencing clinical deterioration despite treatment with AC.
(5) Addition of aspirin or steroids is not recommended due to an association with higher rates of mortality and poor outcome.
(6) Duration of AC treatment: 3–6 months is a reasonable duration of treatment for patients with provoked CSVT; 6–12 months for patients with spontaneous unprovoked CSVT in the absence of a strong permanent thrombophilia; lifelong for patients with a severe thrombophilia (severe genetic deficiency of protein C or S or antithrombin III, homozygous prothrombin or factor V Leiden mutation, antiphospholipid antibody syndrome).

Management guidelines specific to neonatal and pediatric populations have been published, but are limited due to low quality of evidence (14, 20–22). A number of controversies persist, emphasizing the need for more research. As regard the role of thrombophilia testing, there are data in pediatric populations showing that thrombophilias may increase the risk of incident and recurrent CSVT, but it is unknown whether prolonging the duration of AC therapy due to the presence of these conditions alters outcomes (12, 23). As such, the utility of extensive testing for thrombophilia in neonates and children remains uncertain, and deserves further study.

Major uncertainty and controversy exists regarding the treatment of neonates with CSVT. The data from descriptive cohort studies suggest that outcomes are worse among neonates compared to children with CSVT (see **Table 2**). Moreover, in one observational study of neonates, there was a significant incidence of clot propagation and related new infarction in neonates who were not treated with AC (5). Current data suggest that AC therapy in children and newborns is generally safe, but the efficacy is not established (5, 9). Overall recurrence rates are low (<10%) and may be increased in patients not initially treated with AC therapy (23). Existing cohort studies show that AC therapy is less widely practiced for neonates as compared to children (**Table 2**). The less frequent use of AC therapy in neonates likely reflects uncertainty about its safety because of the relatively common occurrence of intracranial bleeding from the birth process, and because of the propensity for newborns to develop hemorrhagic infarcts. Currently, a clinical trial proposal is being developed to evaluate the safety and efficacy of AC therapy in neonates with CSVT (6).

Existing guidelines for managing neonatal and pediatric CSVT reflect these controversies and uncertainties, and are summarized as follows:

(1) American Heart Association Scientific Statement (20): for neonates, consider AC therapy using unfractionated heparin (UFH) or LMWH in cases with prothrombotic disorders, multiple cerebral or systemic thrombi, or a propagating cerebral thrombus after treatment with just supportive measures. For children, it is reasonable to treat with UFH or LMWH in all cases, whether or not there is secondary ICH. Thrombolysis is not recommended in neonates, but may be considered in children.
(2) American College of Chest Physicians (14): for neonates without ICH, consider AC therapy with UFH or LMWH, and treat for 6 weeks to 3 months. For neonates with ICH, treat with AC therapy (UFH or LMWH) initially or postpone treatment until repeat imaging after 5–7 days shows clot propagation. For children with CSVT without ICH, treat with AC therapy (UFH or LMWH), and transition to warfarin if desired for a minimum period of 3 months. Consider longer duration of AC therapy in children with incomplete recanalization or ongoing symptoms. For children with CSVT in the presence of ICH, treat with AC initially or postpone treatment until repeat imaging after 5–7 days shows clot propagation. Thrombolysis or thrombectomy may be considered in children who have severe CSVT and are not responding to AC therapy.
(3) British Committee for Standards in Haemotology (21): these recommendations apply to all age groups. Children with CSVT and no ICH should receive AC therapy with either LMWH or UFH, and continued for a minimum of 3 months in cases of reversible provoking illness (e.g., infection), for 6 months in the absence of provoking illness, and for longer periods of time in patients with a long-lasting or genetic risk factor or with persistent symptomatic venous outflow obstruction. They also recommend that repeat imaging should be considered prior to stopping AC therapy for all patients who have ongoing symptoms referable to venous thrombosis and in patients where assessing extent of recanalization may change decisions about duration of therapy. In children with significant and symptomatic ICH at the time of diagnosis, they recommend it may be reasonable to withhold AC therapy and to repeat imaging at a short interval to evaluate for clot propagation. Those patients with minimal or asymptomatic ICH may be considered for treatment with AC therapy.

Endovascular therapy for CSVT has received increased attention in recent years, as it has attained wide acceptance and greater availability for the treatment of acute arterial ischemic stroke. Several case series have been published reporting results for this therapy in children with CSVT. Mortimer et al. described results of treating 9 children, age 18 months to 16 years, with endovascular

therapies that included catheter-directed thrombolysis, balloon angioplasty, and thrombectomy with the Penumbra device (24). These children were critically ill, mostly comatose, and 8/9 had progressed while on systemic AC therapy. Treatment was successful in achieving partial recanalization in 8/9 cases, none with bleeding complications, and followed by clinical improvement in 8/9 cases. One child died (the one in whom recanalization could not be achieved), and all others survived, with good functional outcomes. Mallick et al. reported that 4 patients, age 18 months to 11 years, among their consecutive cohort of 21 children with CSVT, received catheter-directed thrombolysis for clinical deterioration despite prior treatment with systemic AC therapy (2). Thrombolytic therapy led to full or partial recanalization and clinical improvement in 3 of these cases, while the fourth child died from malignant intracranial hypertension due to extensive treatment-resistant thrombosis. Procedure-related complications occurred in two patients. Waugh et al. described their experience using endovascular catheter-directed infusions of thrombolytic agents in six children with severe life-threatening and progressive CSVT (25). Four of their six patients survived and appeared to benefit, even in the presence of prethrombolytic ICH.

These small case series suggest that endovascular therapy may be helpful in selecting pediatric patients with severely symptomatic, treatment-resistant CSVT. Use of this therapy in children as reflected in these reports is in line with the treatment guidelines proposed for adults. As is the case for any invasive, potentially risky therapy, it would be prudent for providers to account for several factors when considering this therapy for children. First, the potential for procedural complications, and the generally good outcome from standard AC therapy, suggest that endovascular therapy should be reserved for children with severe disease who have failed frontline AC therapy. Second, the procedural risks are likely operator dependent, and so all attempts should be made to involve interventionalists who are experienced in the treatment of children, and that such treatment should occur in a tertiary pediatric center with adequate subspecialty expertise (critical care, anesthesia, vascular neurology, hematology). This is another area where research is needed to more fully characterize the potential for benefit relative to risk in good prospectively ascertained and well-characterized cohorts with long-term follow-up data.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Thrombosis of the Abdominal Veins in Childhood

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Abdominal venous thrombosis is a rare form of venous thromboembolic disease in children. While mortality rates are low, a significant proportion of affected children may suffer long-term morbidity. Additionally, given the infrequency of these thrombi, there is lack of stringent research data and evidence-based treatment guidelines. Nonetheless, pediatric hematologists and other subspecialists are likely to encounter these problems in practice. This review is therefore intended to provide a useful guide on the clinical diagnosis and management of children with these rare forms of venous thromboembolic disease. Herein, we will thus appraise the current knowledge regarding major forms of abdominal venous thrombosis in children. The discussion will focus on the epidemiology, presentation, diagnosis, management, and outcomes of (1) inferior vena cava, (2) portal, (3) mesenteric, (4) hepatic, and (5) renal vein thrombosis.

Keywords: thrombosis, inferior vena cava, portal vein, mesenteric vein, Budd–Chiari, renal vein

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INTRODUCTION

Though rare in children, abdominal venous thromboembolism (VTE) may result in substantial morbidity. In our recent epidemiologic study, there were 4,538 pediatric VTE discharges in 1 year (1). Of these, 17% were abdominal VTE, 44% involved the inferior vena cava (IVC), 36% portal veins, 11% hepatic veins, and 10% were renal vein thrombi. In a prospective study of 466 childhood VTE, 12% were abdominal; 46% of which were in the IVC (2). Thus, 12–17% of childhood VTE is intra-abdominal with IVC thrombosis predominating. High-quality data are limited, thus the following recommendations are based on available literature, expert consensus, and personal experience. The use of anticoagulants in pediatric VTE is comprehensively reviewed in another manuscript in this collection (3).

IVC THROMBOSIS

The majority of IVC thrombi result from extension of ilio-femoral deep vein thrombi (DVT) which, in turn, are a common complication of femoral vein catheterization (4–7). Neonates are prone to catheter-related IVC thrombosis, due to the common utilization of lower extremity and umbilical venous catheters (UVCs). In a Dutch study, 66% of 44 catheter-related thrombi in neonates involved the IVC or right atrium whereas the IVC was not involved in non-catheter-related neonatal VTE (5). In a Canadian registry of catheter-related VTE in children of all ages, IVC involvement was appreciated in 10% of the cohort (6). In the PROTEKT trial, 29% of catheter-related VTE were found in the lower extremity venous system, and one-third of these extended into either the superior or inferior vena cava (7). Thus, it is important to identify the proximal extension of all catheter-related VTE to define the anatomic scope of involvement.

Congenital IVC agenesis/atresia, which has an estimated prevalence of ~0.6%, may present with calcified IVC thrombosis during infancy (8–11). This is most commonly an incidental imaging finding in an asymptomatic infant. However, IVC anomalies occasionally present during adolescence as what initially appears to be unprovoked, proximal lower extremity DVT (12–14). Two recent studies which included adolescents, found that 11–13% of IVC thromboses had evidence of congenital IVC anomaly, whereas none of the control group (cases of lower extremity DVT without IVC involvement) had anomalies (15, 16). In cases of delayed presentation, it is thought that collateral venous drainage is accomplished *via* deep, median, portal, or superficial abdominal veins (17). It is reasonable to hypothesize an anatomic thrombophilia due to increased vascular resistance in these smaller veins, which predisposes to lower extremity DVT. Therefore, it is appropriate to maintain a high index of suspicion for IVC anomalies in children with lower extremity DVT who have no apparent thrombotic predisposition. IVC thrombosis has also been reported following physical abuse and major abdominal surgery in children (18–21).

Doppler ultrasonography, the imaging modality of choice for extremity thrombosis, may miss isolated pathology of the IVC; thus computed tomography (CT) and magnetic resonance scans are preferable (22). Anticoagulant therapy for a period of 3–6 months is appropriate for provoked and unprovoked initial episodes (23). Some authors suggest an initial course of 12 months given concerns for significant post-thrombotic syndrome (PTS) with persistent IVC thrombosis (24, 25). Additionally, some experts advocate thrombolytic therapy as initial treatment (26, 27). It is thought that such an aggressive intervention may decrease the risk for PTS, pulmonary embolism, or acute renal failure (in the setting of suprarenal IVC thrombosis). However, this strategy is based upon expert consensus and thus awaits clinical trial data. Successful IVC stenting followed by aspirin prophylaxis has been reported in children with congenital heart disease and subacute/chronic thrombotic IVC obstruction (28). With regard to IVC agenesis/atresia, IVC reconstruction utilizing polytetrafluoroethylene grafts has demonstrated 83% patency with stable or improved PTS scores at 41 months (29).

Long-term IVC thrombosis outcome has been studied in 39 children who were followed for a maximum of 18 years (24). Six patients (15%) died within 3 months of diagnosis. Twenty-one (53%) presented with extensive thrombosis (defined as involving ≥2 IVC segments or extending into the iliac veins; **Figure 1**). Complete reconstitution of IVC flow was observed in only four (19%) children; three of whom had undergone intervention [thrombolysis (1); surgical (2)]. Persistent caval and/or iliac obstruction was observed in the remaining 17 (81%) patients (6 of whom had been treated with thrombolysis). The remaining 12 (30%) had complete resolution of limited IVC thrombosis on follow-up. PTS was frequent (30%) in those with persistent IVC pathology (24).

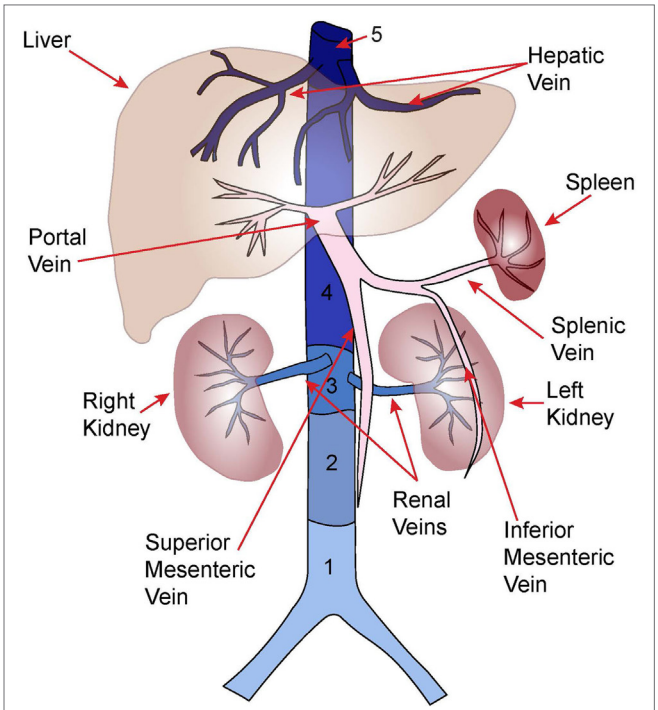

FIGURE 1 | Anatomy of major abdominal veins. Inferior vena cava segments adapted from Ref. (8).

PORTAL VEIN THROMBOSIS (PVT)

Portal vein thrombosis refers to partial or complete occlusion of the portal venous system (**Figure 1**). Thrombus may be restricted to the portal veins or may extend into the splenic and/or superior mesenteric veins. PVT often occurs during the neonatal period with an estimated incidence of 1.3/100,000 live births, and 36/1,000 NICU admissions (9, 30). However, neonatal PVT is often asymptomatic and only identified in the subset of patients who develop symptomatic portal hypertension [e.g., gastrointestinal (GI) bleeding, splenomegaly] several years after the initial thrombotic event (31, 32). Thus, the true incidence is likely higher.

In neonates, UVC placement is the most common cause for PVT. In a retrospective Canadian study of 133 neonates with PVT, 73% were UVC-associated (30). In contrast, incidence of UVC-associated PVT in prospective studies ranges from 0 to 43% (33–37). This variation may be explained by study design differences, diagnostic criteria, and timing of imaging. Other risk factors for neonatal PVT include prolonged catheterization, position of catheter tip, transfusion through the UVC, and sepsis (30, 35, 36). In older children and adults, etiologies of PVT include pancreatitis, cirrhosis, liver transplant, splenectomy, and sickle cell disease (32). Notably, ~50% of childhood PVT has no identifiable etiology (31, 32).

Because neonatal PVT is often asymptomatic, the diagnosis is often an incidental finding of imaging performed for other indications. In the Canadian study, the most common indications for imaging were thrombocytopenia (20%), abdominal distension (17%), elevated liver enzymes (7%), and hepatosplenomegaly (4%) (30). Many cases of neonatal PVT are diagnosed later in childhood secondary to symptoms of portal hypertension. It is estimated that 5–20% of childhood portal hypertension cases are

secondary to PVT (38). In a retrospective study of 108 children with chronic PVT, 52% presented with splenomegaly and 46% with GI hemorrhage (31). Eventually, 79% of the children developed GI bleeding.

Doppler ultrasonography is the most common imaging modality used to diagnose PVT. Acute PVT may be graded ultrasonographically: (a) Grade I: non-occlusive single-branch PVT with normal liver parenchyma, (b) Grade II: occlusive single-branch PVT with normal liver parenchyma, and (c) Grade III: occlusive PVT involving two-branches or occlusive single-branch PVT with liver parenchymal changes (30). An association between Grade III PVT and poor outcome (portal hypertension or liver lobe atrophy) was noted in the original study (30), though a follow-up study failed to confirm this finding (39). Pancreaticoduodenal and peribilliary collaterals may develop around the obstructed veins and are known as "cavernous transformation." This process begins within 5 weeks after the thrombotic event but may take months-to-years to become apparent ultrasonographically (40). Procoagulant defects have been reported in a substantial proportion of patients with PVT (**Table 1**) (9, 39, 41–43). In adolescents with unprovoked PVT, we suggest testing for paroxysmal nocturnal hemoglobinuria and Janus tyrosine-kinase 2 (JAK2) mutations (44, 45).

The utility of anticoagulation for PVT remains unclear since a significant proportion resolve spontaneously. In the Canadian study, 77% of non-occlusive PVT resolved completely or partially whereas only 48% of occlusive PVT resolved. Anticoagulation was administered to 44% of the cohort, but did not appear to influence outcome (30). Similarly, a 70% resolution rate was appreciated for non-occlusive PVT vs. only 31% for occlusive PVT in another study (35). Given the ambiguity surrounding the role of anticoagulation and high rate of spontaneous resolution, there are no consensus guidelines for PVT management (23). Thus, anticoagulation should be considered on a case-by-case basis. In neonates with acute, occlusive PVT and no contraindications, 6–12 weeks of anticoagulation is reasonable. Conversely, in patients who are at risk for bleeding or for non-occlusive PVT, supportive care, and serial ultrasonography monitoring may be appropriate. An expert panel recommends annual screening for evolving portal hypertension for ≥5 years post-diagnosis (38).

Anticoagulation is not indicated for cavernous transformation due to the high rate of variceal bleeding. These children should be referred to gastroenterology for measures to prevent variceal bleeding, which may include: (a) β-adrenergic antagonists, (b) endoscopic variceal band ligation, or (c) endoscopic sclerotherapy

TABLE 1 | Studies investigating the association between thrombophilia and abdominal vein thrombosis.

Reference	Year of publication	Type of study	Subjects tested	Thrombophilia identified (%)	OR (95% CI)
Portal vein thrombosis					
Heller et al. (9)	2000	Case-control	24	FV Leiden: 4 (17%), PC deficiency: 1 (4%), AT deficiency: 1 (4%)	5.47 (1.7–17.6)
El-Karaksy et al. (41)	2003	Case-control	40	FV Leiden: 12 (30%), PC deficiency: 11 (28%), PG20210: 6 (15%), AT deficiency: 1 (3%)	6 (for FV Leiden only)
Morag et al. (39)	2011	Cohort	25	PS deficiency: 2 (8%), FV Leiden: 2 (8%), AT deficiency: 1 (4%)	NA
Pietrobattista et al. (43)	2010	Case-control	31	PC deficiency: 4 (13%), PS deficiency: 4 (13%), PG20210: 3 (10%), FV Leiden: 2 (6%)	11.91 (1.4–100.7)
Ferri et al. (32, 42)	2012	Cohort	32	APLA: 2 (6%), FV Leiden + PG20210:1 (3%)	NA
Neonatal renal vein thrombosis					
Heller et al. (9)	2000	Case-control	31	FV Leiden: 9 (29%), PC deficiency: 2 (7%), AT deficiency: 1 (3%)	10.9 (3.9–31.1)
Kuhle et al. (46)	2004	Cross-sectional	21	FV Leiden: 8 (38%), PG20210 (homozygous): 1 (5%)	NA
Kosch et al. (47)	2004	Case-control	59	FV Leiden: 22 (38%), PG20210: 5 (9%), PC deficiency: 3 (5%), AT deficiency: 3 (5%)	15.6 (7.2–34.2)
Marks et al. (48)	2005	Cohort	28	PC/PS deficiency: 5 (18%), FV Leiden: 5 (18%), PG20210: 1 (4%), AT deficiency: 1 (4%)	NA
Winyard et al. (49)	2006	Cohort	18	FV Leiden: 4 (22%), PC + PS deficiency: 1 (6%)	NA
Hepatic vein thrombosis					
Heller et al. (9)	2000	Case-control	10	FV Leiden: 1 (10%)	3.3 (0.6–18.7)
Nagral et al. (50)	2010	Cohort	16	PC deficiency: 2 (13%)[a], AT deficiency: 1 (6%), APLA: 1 (6%)	NA
Kathuria et al. (51)	2014	Cohort	12	PC deficiency: 6 (50%)[a], PS deficiency: 3 (25%)[a], APLA syndrome: 3 (25%)[b], hyperhomocysteinemia: 2 (17%), AT deficiency: 1 (8%)[a]	NA

PC, protein C; PS, protein S; AT, antithrombin; APLA, anti-phospholipid antibody syndrome; FV Leiden, Factor V Leiden mutation (FV R506Q); PG20210, prothrombin gene mutation (FII G20210A); NA, not applicable.

[a]Low PC, PS, and AT levels may be acquired in the setting of advanced liver disease.

[b]Unclear if abnormal labs were repeated 12 weeks apart to confirm APLA syndrome. Note: pediatric data regarding the association of thrombophilia with IVC thrombosis/atresia and mesenteric vein thrombosis not available.

(52). Creation of a vascular shunt between the mesenteric vein and left portal vein (Rex shunt) can reduce portal hypertension and restore portal venous flow through the liver (52). Rex shunts are associated with improved growth and cognitive performance, decreased hypersplenism, and prevention of hepatopulmonary syndrome (53–55). Rex shunts are thus recommended for both primary and secondary prophylaxis of variceal bleeding in children with portal hypertension (56).

MESENTERIC VEIN THROMBOSIS (MVT)

Mesenteric vein thrombosis (**Figure 1**) is exceedingly rare in children with literature limited to case reports and series (57–60). Pancreatitis, surgery, trauma, and oral contraceptives have been associated with pediatric MVT. Early detection and aggressive management are imperative to prevent thrombus progression, bowel infarction, and death (58).

Symptoms of acute MVT are dependent on thrombus size and location, as well as depth of bowel-wall ischemia and include abdominal pain, tenderness, nausea, vomiting, diarrhea, and hematochezia (61). Lactic acidosis may be seen late in the disease course, after bowel infarction has ensued. Early diagnosis is dependent on appropriate imaging studies in symptomatic patients. Plain films are typically non-specific but may include dilated, thickened bowel loops, and multiple air-fluid levels suggestive of ileus. Pneumatosis intestinalis, portal vein gas, and free peritoneal air may be seen later and are characteristic of bowel infarction (61). Doppler ultrasonography may be attempted, but it is often insufficient to adequately evaluate the mesenteric vein. Thus, CT with contrast is preferred and able to confirm the diagnosis in ~90% of cases (62). CT may simultaneously evaluate for bowel infarction and extent.

The rarity of pediatric MVT impairs the development of evidence-based treatment guidelines. In general, management includes exploratory laparotomy with resection of necrotic bowel followed by post-operative anticoagulation. Multiple adult studies have demonstrated that anticoagulation is effective in recanalization of acute MVT and in preventing thrombus progression and recurrence (63–65). Thus, consensus guidelines endorse early anticoagulation for acute MVT in adults; but do not specify duration of therapy (66). In children, we suggest 3 months of anticoagulation for clearly provoked clots, and 6–12 months of therapy for unprovoked clots (or if the initial risk factor is unresolved). There are insufficient data to support thrombolytic therapy for pediatric MVT.

BUDD–CHIARI SYNDROME (BCS) (HEPATIC VEIN THROMBOSIS)

Budd–Chiari syndrome is most commonly diagnosed in adults and results from hepatic venous outflow tract obstruction (50, 67). In adults, the obstruction may occur secondary to extrinsic compression of the hepatic veins or hepatic segment of the IVC (segment 5; **Figure 1**), most commonly by the mass effect of hepatocellular carcinoma, whereas primary thrombosis is often secondary to JAK2 mutated myeloproliferative disease (~50% of cases) (67). In children, obstruction of the hepatic veins with or without obstruction of IVC segment 5 has been described. The obstruction may occur due to a membrane occluding the vascular lumen, the origins of which are debated (50, 68). An autopsy study of the histopathology of this lesion in adults suggests that the membrane is composed of a fibrous laminar structure derived from organized subacute and chronic thrombi, suggesting thrombotic disease as the underlying etiology (69). This impression is consistent with observations that severe thrombophilias (e.g., antithrombin deficiency, protein C deficiency, JAK2 mutations) are more common than expected in both adult and pediatric series (**Table 1**) (50, 51, 70). In the case of membranous obstruction, thrombosis is thought to evolve from venostasis; whereas in the case of primary IVC thrombosis, hepatic vein thrombosis may arise secondary to direct extension of thrombus into the intrahepatic vessels. Other causes of hepatic venous obstruction, including sinusoidal obstruction syndrome, should be excluded. BCS is uniformly fatal without treatment (67).

In both pediatric and adult BCS, there is a male predominance, which in pediatrics is ~1.8 male:female (51). Most cases present with subacute or chronic symptoms that include insidious onset of abdominal distention (ascites), abdominal wall collateral veins, and portal hypertension (50, 51, 68). Less common symptoms include GI bleeding, lower extremity edema, jaundice, hepatosplenomegaly, or liver failure (in the acute or fulminant form of the disease) (50, 51, 68). Pediatric BCS has been reported as a complication of liver transplantation, ventriculoatrial shunt placement, and major abdominal surgery as well as medical conditions such as nephrotic syndrome (NS), ulcerative colitis, and liver abscess (50, 71–75).

Doppler ultrasonography has a diagnostic sensitivity of over 85% and is considered to be the frontline imaging modality for BCS (76, 77). CT and MRI scans are usually reserved for inconclusive cases. Rarely, when a diagnosis cannot be established by non-invasive imaging modalities, the patient may need venography and/or liver biopsy (78). There are no well-designed trials of anticoagulant therapy (without procedural intervention) for BCS in adults or children (50, 67). In adults, there is retrospective data suggesting a beneficial effect, but this is likely restricted to patients with less severe disease (67, 79, 80). Meanwhile, in children, the anecdotal experience has been disappointing (50). Interventional modalities are thus favored, with several pediatric series reporting promising results (50, 51, 81, 82). Potential interventions include balloon venoplasty, stent placement, mesocaval shunt, portocaval shunt, pericardial patch reconstruction, and transjugular intrahepatic portosystemic shunt (TIPS). The favored approach is dependent upon the extent of pathology; with venoplasty/stent placement favored for patients with short-segment obstructions whereas TIPS is favored in those with long-segment obstructions (51). Regardless of the approach, long-term anticoagulant or antiplatelet therapy is indicated post-procedure to maintain patency. For patients presenting with fulminant hepatic failure or failing intervention, liver transplantation may be lifesaving. Although there are no outcomes data from well-designed pediatric trials of these interventions, in adults their use has resulted in improved survival to 80% at 5 years (67).

RENAL VEIN THROMBOSIS (RVT)

Renal vein thrombosis (**Figure 1**) is principally a neonatal disease accounting for 15–20% of neonatal VTE (46, 83, 84). The incidence of neonatal RVT is ~2.2/100,000 live births, and 0.5/1,000 NICU admissions (84, 85). Low renal perfusion pressure, natural anticoagulant deficiency, and renal venous anatomy predispose the neonatal kidney to thrombosis (86). Neonatal RVT originates in the arcuate and interlobular veins with subsequent extension to involve the main renal veins and/or IVC (87). Maternal risk factors for neonatal RVT include diabetes, hypertension, and polyhydramnios; whereas patient risk factors include perinatal asphyxia, hypotension, sepsis, congenital heart disease, and thrombophilia. Neonatal RVT is the most common non-catheter associated VTE in neonates, though UVCs are reported in 15–17% of cases (46, 48).

In older children, RVT has been associated with NS and renal transplantation. The incidence of VTE in adult NS is ~27% with RVT developing in 31%; the highest incidence of RVT (37%) occurring in those with membranous nephropathy (88). In contrast, VTE occurs in only (3%) of childhood-NS cases of which (10%) are RVT, possibly because membranous nephropathy is rare in children (88, 89). It is thought that NS creates an imbalance between urinary loss and synthetic compensation of hemostasis-related proteins (88). In pediatric renal transplantation, RVT has emerged as a leading cause of graft failure (21%) (90). Young recipient age, previous transplant, and pre-transplant peritoneal dialysis are predisposing risk factors.

Most cases of neonatal RVT (67%) are diagnosed within the first 3 days of life (46, 49, 91). Cardinal signs include macroscopic hematuria, thrombocytopenia, and palpable abdominal mass, though the complete triad is seen in only 13–22% of cases (49, 91, 92). Over 50% of cases are associated with varying degrees of renal dysfunction (48). Neonatal RVT is more common in males (67%) and most often unilateral (70%) [left predominant (64%)] (91). IVC extension occurs in 44 and 15% have ipsilateral adrenal hemorrhage.

Neonatal RVT diagnosis requires a high index of suspicion and appropriate imaging. Doppler ultrasonography is the modality of choice and progression of imaging findings have been described (86, 93). Initially, the affected kidney is enlarged with loss of cortico-medullary differentiation and perivascular echogenic streaking thought to be representative of thrombus within the arcuate and interlobular veins. Subsequently, thrombosis may be seen in the renal vein and IVC. Eventually, a significant proportion of kidneys become atrophic. Initial kidney dimensions may be predictive of outcome (49). Each 1 mm increase in kidney length predicts a 3 mL/min/1.73m^2 loss in glomerular filtration rate; such that kidneys > 6 cm at presentation are rarely salvageable.

Multiple studies have noted a high prevalence of thrombophilic traits (43–68%) in neonates with RVT, particularly FV Leiden (**Table 1**) (9, 46–49). Neonatal RVT is associated with significant morbidity (91). At 3.7 years, 71% develop renal atrophy, 19% develop hypertension, and 3% require renal replacement therapy. The role of anticoagulation in preventing these complications remains unclear (92). In a study of 23 neonates with RVT, 33% of those receiving heparin developed renal atrophy, compared with 100% in those receiving no anticoagulation. However, subsequent studies revealed no anticoagulation-dependent difference in outcome (85, 91). Current consensus guideline recommendations are: (a) supportive care with serial imaging vs. 6–12 weeks anticoagulation for unilateral RVT with no renal dysfunction and no IVC extension, (b) 6–12 weeks anticoagulation for unilateral RVT with extension into the IVC, and (c) thrombolysis followed by anticoagulation vs. anticoagulation alone for bilateral RVT with evidence of renal dysfunction (23). An expert panel has proposed an RVT risk assessment scale and recommends that the patients be reevaluated biannually for ≥5 years to assess renal function (38).

CONCLUSION

Intra-abdominal VTE is infrequent in children. When present, however, they are associated with significant morbidity. The incidence of thrombophilia may be high, thus the risks and benefits of thrombophilia testing should be carefully considered with the patient and family. The approach to therapy is guided by the involved veins and may include thrombolysis, surgery, and/or anticoagulation and warrants a multi-disciplinary approach involving pediatric hematology, interventional radiology, and relevant sub-specialties.

AUTHOR CONTRIBUTIONS

Both authors reviewed the literature, wrote, and edited the manuscript. RK wrote the first draft of the Portal, Mesenteric, and Renal Vein sections. BK wrote the first draft of the IVC and Budd–Chiari sections.

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MINI REVIEW
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Neonatal Venous Thromboembolism

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Neonates are the pediatric population at highest risk for development of venous thromboembolism (VTE), and the incidence of VTE in the neonatal population is increasing. This is especially true in the critically ill population. Several large studies indicate that the incidence of neonatal VTE is up almost threefold in the last two decades. Central lines, fluid fluctuations, sepsis, liver dysfunction, and inflammation contribute to the risk profile for VTE development in ill neonates. In addition, the neonatal hemostatic system is different from that of older children and adults. Platelet function, pro- and anticoagulant proteins concentrations, and fibrinolytic pathway protein concentrations are developmentally regulated and generate a hemostatic homeostasis that is unique to the neonatal time period. The clinical picture of a critically ill neonate combined with the physiologically distinct neonatal hemostatic system easily fulfills the criteria for Virchow's triad with venous stasis, hypercoagulability, and endothelial injury and puts the neonatal patient at risk for VTE development. The presentation of a VTE in a neonate is similar to that of older children or adults and is dependent upon location of the VTE. Ultrasound is the most common diagnostic tool employed in identifying neonatal VTE, but relatively small vessels of the neonate as well as frequent low pulse pressure can make ultrasound less reliable. The diagnosis of a thrombophilic disorder in the neonatal population is unlikely to change management or outcome, and the role of thrombophilia testing in this population requires further study. Treatment of neonatal VTE is aimed at reducing VTE-associated morbidity and mortality. Recommendations for treating, though, cannot be extrapolated from guidelines for older children or adults. Neonates are at risk for bleeding complications, particularly younger neonates with more fragile intracranial vessels. Developmental alterations in the coagulation proteins as well as unique pharmacokinetics must also be taken into consideration when recommending VTE treatment. In this review, epidemiology of neonatal VTE, pathophysiology of neonatal VTE with particular attention to the developmental hemostatic system, diagnostic evaluations of neonatal VTE, and treatment guidelines for neonatal VTE will be reviewed.

Keywords: developmental hemostasis, neonatal thrombosis, thrombophilia, neonatal venous thromboembolism, renal vein thrombosis

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INTRODUCTION

Venous thromboembolism (VTE) is increasingly recognized and diagnosed in the neonatal population. The neonatal patient is at risk for VTE due to a combination of factors that can easily tip the hemostatic balance toward thrombosis such as invasive medical procedures, systemic inflammation, central venous catheters (CVCs), fluid fluctuations, and infection. In addition, the developing hemostatic system may be more vulnerable to disruptions and may more easily shift toward thrombosis.

Improved attention to and recognition of VTE symptoms is also resulting in an increased incidence of neonatal VTE. Data are still limited with regard to optimal diagnosis and management of VTE as well as prevention of VTE in the neonatal population.

EPIDEMIOLOGY

Venous thromboembolism is a relatively rare disease in the pediatric age group. However, VTE is increasingly considered and diagnosed in pediatric patients. Canadian registry data from the early 1990s indicated a VTE incidence of 5.3 per 10,000 hospital admissions and an overall incidence of 0.07 per 10,000 children (1). Subsequent studies have highlighted the increasing incidence in the last decade, with as much as a 70% increase of VTE incidence from 2001 to 2007 (2). In a retrospective cohort study of the Pediatric Health Information System (PHIS) database, the incidence of VTE increased from 34 per 10,000 hospital admissions in 2001 to 58 per 10,000 hospital admissions in 2007. For PHIS database, patients less than 28 days old, the VTE incidence was approximately 75 per 10,000 hospital admissions (2). The distribution of VTE across the pediatric age group has been reported to be bimodal, with one spike in incidence in the neonatal period and a second spike in the adolescent period (1, 2). However, some studies have suggested that this bimodal distribution disappears when the data are standardized for a number of discharges or a number of admissions, and instead show an overall increased incidence of VTE with age (3, 4). Regardless, the incidence of VTE in the neonatal population remains high and is increasing (2, 5) and warrants continued investigation with regard to diagnosis, prevention, and management.

DEVELOPMENTAL HEMOSTASIS

The neonatal hemostatic system is both quantitatively and qualitatively distinct from that of an older child or adult. The term "developmental hemostasis" has been applied to the period of time when the neonatal hemostatic system exists in an evolving balance of pro- and anticoagulant factors (6). Neonatal levels of factor VII, fibrinogen, and alpha-1 antitrypsin are similar to older children and adults, but all other pro- and anticoagulant proteins are deficient in neonates on day of life one and reach adult values by around 6 months of age (6). Neonatal levels of the anticoagulants, ATIII, protein C, and proteins S are similar to the levels of individuals with heterozygous deficiencies (6, 7). Differences in the hemostatic system are magnified in premature infants; yet, hemostatic system maturation is accelerated as compared to term infants (8). Despite the decreased pro-coagulant levels and the decreased anticoagulant levels, the healthy newborn is believed to exist in a hemostatic balance, neither prone to hemorrhage nor thrombosis (7). However, the balance is delicate and can be easily tipped in either direction (7).

RISK FACTORS

Acquired Risk Factors

The neonatal hemostatic system can be tipped toward thrombosis by a variety of acquired risk factors, and greater than 95% of neonatal VTE is associated with at least one clinical risk factor (5, 9) (**Table 1**). The most common clinical risk factor is the presence of a CVC (5, 9–13). A prospective study of neonates who underwent CVC placement indicated a 13% incidence of CVC-associated VTE (14), while another evaluating only umbilical catheter revealed a higher incidence of 22% (15). A recent systematic review of the literature noted that risk factors for CVC thrombosis development are not reliably documented across studies, however; birth weight, gestational age, prolonged catheter duration (>6 days), umbilical venous catheter (UVC) mal-placement, and the addition of blood products to UVC infusions were all highlighted as risk factors for CVC-related thromboses (5, 16).

TABLE 1 | Risk factors for venous thromboembolism (VTE) development in neonates.

Maternal risk factors	Neonatal risk factors	Risk factors specific to central venous catheter (CVC)-related VTE
Infection	CVC	Low birth weight
Placental disease	Sepsis	Prematurity
Diabetes mellitus	Congenital heart disease	Prolonged catheter duration (>6 days)
Hypertension	Perinatal asphyxia	Umbilical venous catheter (UVC) mal-placement
Pre-eclampsia	Dehydration	Addition of blood products to UVC
Dyslipidemia		Mechanical ventilation
Metabolic syndrome		Surgery
Antiphospholipid antibody syndrome		
Emergent C-section		
Premature rupture of membranes		
Inherited thrombophilia		

In addition to CVCs, sepsis, mechanical ventilation, perinatal asphyxia, congenital heart disease, and dehydration are recognized risk factors for neonatal VTE (11, 13, 17). The contribution of maternal risk factors to neonatal VTE development is not as well studied, however; infection, placental disease, diabetes mellitus, hypertension, pre-eclampsia, dyslipidemia, metabolic syndrome, antiphospholipid antibody syndrome, inherited thrombophilia, emergent Cesarean section, and premature rupture of membranes have been associated with increased risk of neonatal VTE (18). At least one or more maternal risk factor for neonatal VTE has been found in up to 56% of neonates with venous thrombosis (18). Risk factors for renal vein thrombosis (RVT) are similar to other neonatal VTE risk factors and include prematurity, maternal diabetes, dehydration, infection, perinatal asphyxia, and umbilical vein catheter (13, 19). The pathophysiology is suggested to result from impaired renal perfusion under the listed clinical circumstances, which leads to vasoconstriction and subsequent impaired venous blood flow which puts the postglomerular circulation at increased risk for thrombosis (20).

Inherited Thrombophilia

The role of inherited thrombophilic risk factors in neonatal VTE development is poorly defined (21). A recent systematic review

analyzed 13 publications from 2008 to 2014 evaluating the role of inherited thrombophilia in neonatal VTE development and treatment. The authors concluded that neonatal VTE is multifactorial and clinical risk factors weigh more heavily on the prothrombotic scale than inherited thrombophilia, particularly in CVC-associated VTE (9). In an earlier study, the overall prevalence of inherited thrombophilia in neonates with VTE was not different than that of the healthy population, concluding that screening neonates with VTE for inherited thrombophilia was not necessary (12). In contrast, in another study of catheter-related VTE, 15 of 18 infants with VTE had at least one inherited thrombophilia (10). Further, in an Italian registry of neonatal VTE, an inherited thrombophilia was found in 33% of infants with an "early-onset" VTE (VTE in the first day of life) (18). While inherited thrombophilia appears to be present in some neonates with VTE, both CVC related and not, the role of inherited thrombophilia testing in neonates with VTE remains up for debate as it does not appear, at this time, to influence type or duration of treatment (9).

CLINICAL PRESENTATION

Neonatal VTE most commonly occurs in the hospital, in the neonatal intensive care unit, as a reflection or effect of more significant illness. However, neonatal VTE can be the admitting diagnosis for neonates, as in RVT or cerebral sinus venous thrombosis (CSVT). Signs and symptoms of VTE in neonates are dependent upon the VTE location. A recent publication detailing data from a multicenter network of Italian investigators noted that of the 75 neonatal thromboses, 57 (76%) were associated with symptoms at diagnosis. For the VTE cases, 31/41 thromboses were associated with symptoms such as edema (50%), limb discoloration (34%), abdominal mass (10%), and central venous line dysfunction (7%) (18). The remaining thromboses were found incidentally on imaging obtained for other reasons (18). Symptoms of RVT include hematuria, abdominal mass, and/or thrombocytopenia. CSVT symptoms include seizures, apnea, agitation, decreased alertness, and symptoms of infection (22). The non-specific symptoms of respiratory failure, apnea and bradycardia, thrombocytopenia, and persistent bacteremia have also all been reported as symptoms of VTE (11).

Premature infants are more likely to be diagnosed with a VTE than term infants (21). In the above mentioned Italian registry study, preterm neonates accounted for 71% of thromboses (18). Timing of diagnosis is related both to gestational age and to site of thrombosis. In a registry of pediatric hospitals in Germany, venous thrombosis diagnosis at day of life 11 or 12 was more common than diagnosis at birth (17). RVT was more commonly diagnosed soon after birth in term infants but later (day 8 of life) in premature infants (17). In the Canadian registry, spontaneous RVT was more common in term infants while all other thromboses were found across gestational ages (11). Differences in timing of VTE presentation between premature and term neonates are likely related to acquired VTE risk factors related to underlying illness and intensive care.

Diagnostic Imaging

Imaging modalities employed to diagnose VTE in neonates include ultrasound, venography, computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound is the most common imaging modality employed to diagnose neonatal VTE, although venography is considered the reference standard for diagnosis of VTE (23). In the Canadian VTE registry study, Doppler ultrasound was used to diagnose 67% of the venous thromboses (11). Similarly, Doppler ultrasound was the most common imaging modality in the German VTE registry study (17). The availability of Doppler ultrasound as well as its non-invasive nature makes it an attractive diagnostic modality. However, it is operator dependent and its sensitivity and specificity decline when evaluating intrathoracic vessels as well as the iliac vessels or if the patient is edematous or has interfering skin abnormalities (23). A prospective study aimed at determining the incidence of asymptomatic venous thromboses associated with UVCs found that Doppler echocardiography was less sensitive than contrast venography (24). Further, the Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase study recommended a combination of ultrasound and venography to investigate upper extremity, line associated VTE (25). Venography is not often employed, though, given its invasive nature, technical demands, and radiation exposure (23). CT or MRI can be employed to evaluate the intrathoracic venous system for thromboses (26). A reasonable approach may be to start with ultrasound, and if negative and clinical suspicion remains high, then pursue evaluation with MRI or CT depending on diagnostic modality availability and contributing clinical factors.

TREATMENT

Treatment of neonatal VTE cannot simply be extrapolated from recommendations for adult VTE as the neonatal hemostatic system, the neonatal vascular system, and neonatal co-morbidities create a delicate balance of hemorrhage and thrombosis. The severity of the thrombosis, the possibility of organ or limb impairment, the presence of comorbidities such as congenital heart disease, and the bleeding risk all influence the decision to treat or to observe (27). Randomized trials evaluating type and duration of treatment are lacking in the neonatal population, and treatment decisions are largely based on consensus evidence-based guidelines (28). The CHEST guidelines provide recommendations for a variety of thrombotic complications in the neonatal population, including RVT and CVC-associated thromboses (28). The CHEST guidelines will not be extensively reviewed here as they are accessible through online journals.

Antithrombotic therapy is aimed at reducing the risk of extension or embolization, to reduce the risk of recurrence, and to reduce the risk of postthrombotic syndrome (PTS) (29). Duration of anticoagulation is generally 3 months for provoked thromboses and may be up to 6 months for idiopathic thromboses (26). The anticoagulants most commonly used in treatment of neonatal VTE include unfractionated heparin (UFH) and low molecular weight heparin (LMWH). Developmental hemostasis, differences in drug metabolism, and unique comorbidities must weigh into the choice of anticoagulant. Both UFH and LMWH require higher doses in neonates than older children and adults to achieve therapeutic levels. A prospective study, which included full term and premature neonates, found LMWH to be a safe and

effective form of anticoagulation (30). The advantages of LMWH include subcutaneous administration, more predictable pharmacokinetic profile, minimal monitoring requirements, and less bleeding risks (27). The advantages of UFH include potentially easier reversibility with protamine. A recent Cochrane review of heparin (both UFH and LMWH) for the treatment of thrombosis in neonates found no eligible publications for inclusion in their review and concluded that there are no trials to recommend or refute the use of heparin for treatment of neonates with thrombosis (31).

Vitamin K antagonists (VKAs) are difficult to use in the neonatal period owing to a variety of factors such as frequent monitoring, lack of liquid formulation, and naturally low levels of vitamin K dependent factors (27). In addition, formula is supplemented with vitamin K, perhaps negating some of the effects of VKA and breast milk is deficient in vitamin K, perhaps putting the breastfed infant at greater bleeding risk (27). A single randomized control trial comparing LMWH and UFH followed by VKA has been conducted and demonstrated that LMWH was effective for treatment of VTE and was not inferior to UFH/VKA in pediatric patients. Neonates were not included in the study (32). VKA treatment is generally not favored in the neonatal population, and either UFH or LMWH are more commonly employed. None of the direct oral anticoagulants has been approved in pediatric populations, however; studies are ongoing in the pediatric population for these new anticoagulants (33).

Drug Dosing and Monitoring

Therapeutic monitoring of UFH is recommended with a goal anti-Xa level of 0.35–0.7 units/mL (28). It is suggested that UFH boluses should not be greater than 75–100 units/kg and should be avoided in those children where a significant bleeding risk exists (28). CHEST guidelines recommend starting the initial infusion at 28 units/kg per hour for infants but individual risk factors should be considered when choosing initial dosing (28). Neonatal dosing of LMWH is higher than older children and adults, and frequently doses of 1.5–2 mg/kg twice daily are needed to get into the therapeutic anti-Xa range of 0.5–1 units/mL (28, 34–36).

Thrombolysis

Thrombolytic therapy employs different agents [tissue plasminogen activator (tPA), streptokinase, urokinase] to convert plasminogen to plasmin, which ultimately cleaves fibrinogen and fibrin to fibrinogen/fibrin-degradation products (27). The decreased plasminogen concentration in neonates may decrease the efficacy of these agents, though (27). On the other side, the delicate neonatal cerebral vasculature and immaturity of the hemostatic system may predispose the infant to bleeding complications. A retrospective review of thrombolysis from 1964 to 1995 identified that intracranial hemorrhage occurred in 1/83 term infants and 11/86 preterm infants receiving tPA (37). In another review of 16 neonates treated with tPA, 7 had complete resolution of their thrombosis while 7 had partial resolution. One neonate died while receiving tPA from massive intracranial hemorrhage, but tPA was given despite severe thrombocytopenia in this patient, which was thought to be a confounding factor in the patient's bleeding (38). Current consensus guidelines recommend against thrombolysis therapy unless the thrombosis is life-, limb-, or organ-threatening (28). If thrombolysis is used, tPA is the recommended agent, and plasminogen administration (through transfusion of fresh frozen plasma) is recommend prior to beginning thrombolysis (28).

MORBIDITY/MORTALITY

Mortality

Data regarding morbidity and mortality of VTE in neonates are lacking as follow-up in the majority of registry studies is short. In the Canadian registry, mortality in neonates with RVT was 5%, with other venous thrombosis was 18%, and with arterial thrombosis was 21%. However, all deaths were not directly attributable to the thromboses (11). The mortality rates for both aortic and right atrial/superior vena cava thromboses were 33% (11). In further analysis of the outcomes in the Canadian registry, for children 1 month to 18 years, the all-cause mortality was 16% with a thrombosis-related mortality of 2.2% (39). In the German registry study, 9% (7/79) of neonates with thromboses died, with three of the deaths related to thrombosis (17).

Recurrence

Recurrence rates are also difficult to determine accurately due to short follow-up times in most studies. The recurrence rate in the Canadian registry for children >1 month was 8.1% (39). The role of inherited thrombophilia on recurrent VTE is variable. Some studies suggest that the most important risk factor of recurrent thromboses is the presence of a clinical risk factor or the recurrence of the original clinical risk factor (12). However, other authors suggest that the presence of inherited thrombophilias, especially in combination, are risk factors for recurrent thrombosis and thus advocate their screening (40–42). Guidelines regarding the implementation of pharmacologic prophylaxis are lacking, and thus as no treatment change is currently recommended due to the presence of an inherited thrombophilia, testing for an inherited thrombophilia should be performed on an individual basis or, ideally, in the context of a clinical study.

Postthrombotic Syndrome

Postthrombotic syndrome is a chronic complication of deep vein thrombosis and is characterized by chronic venous insufficiency. PTS results from a combination of residual thrombus causing obstruction and secondary valvular reflux (43). The data on neonates are lacking owing to variability in duration of follow-up in most of the studies and registries. In a retrospective study of children with upper extremity VTE, 16% of neonates developed mild PTS with collateral vein formation and increased extremity circumference. Lack of clot resolution and extension of the clot were identified as risk factors for PTS development (44). In the Canadian registry, PTS was diagnosed in 12.4% of the children with VTE (39). Data support the use of thrombolytic regimens in treatment of acute lower extremity DVT to reduce the risk of PTS in older children, but data are lacking in neonates (45).

Heparin-Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia is a drug-induced, immune-mediated thrombocytopenia that is associated with the potential for serious thrombotic complications (46). The thrombocytopenia is typically moderate and the bleeding risk is low, however; the thrombosis risk is high (47). There is little literature on the development of HIT in the pediatric population, but the incidence is likely lower in children than in adults (46). The lower incidence is thought to be secondary to age-dependent differences in both the coagulation and immune systems (46). A recent review of the pediatric HIT literature reported an incidence between 0 and 1.7% in the neonatal subpopulation of anti-PF4/heparin antibodies but no cases of neonatal HIT (47). Further studies are needed to better understand HIT in the neonatal population. Given its significant deleterious outcomes, if suspected, all heparin should be stopped and a non-heparin alternative, such as a direct thrombin inhibitor (DTI), should be started until HIT is ruled out (48). Argatroban is the only DTI that has been prospectively studied in pediatric patients with HIT, and dosing guidelines are now included in the prescribing information (49, 50).

CONCLUSION

Venous thromboembolism in the neonatal population is a distinct pathophysiological entity, requiring age-specific therapy and careful follow-up. Long-term follow-up studies are needed to more fully understand the impact of neonatal VTE diagnosis on patients as they age. A few special circumstances may require heightened attention such as patients who need long-term or repeated central venous access, the risk of PTS in the growing neonate, and the risk of recurrence for females who someday require estrogen therapy. There are many unknowns in the realm of neonatal VTE, which creates an excellent opportunity for research and investigation to improve our understanding of risks, treatments, and long-term management. Long-term registry data are needed in order to follow neonates who develop VTE more closely to obtain better information on morbidity and mortality acutely and chronically.

AUTHOR CONTRIBUTIONS

KH performed the literature review and wrote the manuscript.

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Venous Thromboembolism in Pediatric Vascular Anomalies

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The presence of a vascular anomaly suggests that capillaries, veins, arteries, and/or lymphatic vessels have demonstrated abnormal development and growth. Often dilated and misshaped, these vessels augment normal flow of blood and lymphatic fluids that increases the overall risk to develop intralesional thrombosis. Abnormal endothelial and lymphoendothelial cells activate hemostasis and hyperfibrinolytic pathways through poorly understood mechanisms, which contribute to the development of localized intravascular coagulopathy. Vascular malformations, tumors, and complex combined syndromes demonstrate varying degrees of prothrombotic activity and consumptive coagulopathy depending on the vessels involved and the pattern and extent of abnormal growth. The clinical impact of venous thromboembolism in pediatric vascular anomalies varies from painful syndromes that disrupt quality of life to life-threatening embolic disease. There remains little literature on the study, evaluation, and treatment of thrombosis in pediatric vascular anomalies. However, there have been great advances in our ability to image complex lesions, to surgically and interventionally augment disease, and to provide enhanced supportive care including patient education, compression therapy, and strategic use of anticoagulation.

Keywords: vascular malformation, venous thromboembolism, sclerotherapy, vascular tumor, vascular anomaly

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INTRODUCTION

Pediatric vascular anomalies affect roughly 5% of the population and consist of abnormally developed and misshaped capillaries, veins, arteries, and/or lymphatic vessels. They demonstrate irregular flow of blood and lymphatic fluids, consist of malformed and overly activated endothelial walls, and can carry an increased risk for intralesional and/or systemic thrombosis. The clinical impact of thrombosis in pediatric vascular anomalies ranges from mild episodic pain associated with small superficial thrombi to life-threatening sequela of embolic thrombi formed *via* connections to deeper ectatic vessels (1). The chronic formation and lysis of thrombi can progressively worsen pain and increase lesion size as the vessel walls lose elasticity. These complications can substantially limit daily activities and the negative impact on a child's quality of life directly contributes to a family's decision to pursue aggressive therapeutic interventions. A multidisciplinary approach is recommended to treat all vascular anomalies, and the morbidity and mortality associated with thrombotic complications dictates the need to include a physician familiar with pediatric hematology as part of this multidisciplinary team.

Vascular anomalies are divided between vascular malformations (congenitally malformed vessels) and vascular tumors (acquired proliferating growths of endothelial and lymphendothelial origin) (2). The International Society for the Study of Vascular Anomalies (ISSVA) has advocated

for the use of this standardized nomenclature to help facilitate diagnosis and reduce treatment inconsistences (3). Although very few publications exist that study the development of venous thromboembolism (VTE) in vascular anomalies, vascular malformations, specifically venous malformations (VMs), have been shown to demonstrate a high frequency of acquired thrombosis. A number of vascular tumors have been associated with a variety of local and systemic coagulopathies. However, if present, they tend to be associated with hemorrhagic complications and to a much lesser degree thrombotic complications. The aim of the current article is to summarize the published clinical experience with and treatment of VTE in pediatric vascular anomalies, specifically highlighting those associated with VMs.

VASCULAR MALFORMATIONS

Vascular malformations, the abnormal congenital development of capillaries, veins, arteries, and lymphatics, have historically been difficult to diagnose and classify. Vascular malformations are now classified according to flow velocity (documented by Doppler ultrasonography) and by the predominant vessel types involved. Slow-flow (or low-flow) lesions consist of capillaries, veins, and/or lymphatics. Fast-flow (or high-flow) lesions include arteriovenous malformations and aneurysms (3, 4). Although Doppler ultrasonography plays an important role to classify a lesion, magnetic resonance imaging (MRI) is the most accurate imaging modality to define the extent of a vascular malformation and is essential to obtain prior to any interventional therapy (5). Clinical history and exam should be utilized as adjuvant tools to accurately diagnose a child's vascular malformation.

Venous Malformations

Venous malformations develop from congenital errors in vascular morphogenesis. Amongst all vascular malformations, the slow-flow lesions, most prominently venous, lymphovenous (LVM), and capillary-lymphovenous (CLVM) malformations, demonstrate the highest incidence of baseline coagulation abnormalities with increased risk for thrombosis in both children and adults. VMs are present at birth and can greatly vary in location, size, depth, and degree of ectasia. The defective and dilated veins demonstrate irregularly attenuated walls that, histologically, have decreased smooth muscle cells and are lined only by endothelial cells (6, 7). Skin overlying a VM often demonstrates a marked bluish discoloration often confused for a bruise at birth. They are soft and compressible on exam. VMs will demonstrate bright hyperintensity on spin-echo T2-weighted MRI sequences with fat suppression (6). The blood flow through VMs is disrupted, turbulent, and stagnant at times. Vessel injury and inflammation activate endothelial cells, activate coagulation and consumption of clotting factors, and generate thrombin and fibrin (8, 9). This unique chronic consumptive coagulopathy, coined localized intravascular coagulation (LIC), is characterized by decreased levels of plasma fibrinogen, factor V, factor VIII, factor XIII, and increased D-dimer (10). LIC increases a child's risk for intralesional thrombosis and their peri-surgical/procedural risk for severe hemorrhage. VMs with LIC demonstrate all of the components of Virchow's triad including stasis of blood flow, injury to vascular wall, and activation of the coagulation cascade. Virchow's triad is widely accepted to define high risk factors that, when combined, result in the development of VTE. The extent of the VM correlates with the severity of the LIC and overall risk for thrombosis formation (6, 8).

As a child ages, VMs swell and can become bulky depending on location and a patient's mobility. Chronic intralesional thrombosis results in further deformation of the lesion and contributes to ongoing inflammation and chronic pain. With abnormal fibrinolysis, superficial and intralesional thrombi are not adequately cleared. The chronic thrombi bind calcium deposits and form hard, round thrombi termed phleboliths. Phleboliths are often palpable, painful, easily identifiable on imaging, and can greatly impair function. Phleboliths of the lower extremities, for example, may impact a child's ability to ambulate. On MRI, phleboliths present as low-intensity signals on T1 and T2 images.

Venous malformations can be further classified according to Puig et al. into four types based on their venographic appearance/drainage (11). Type 1 is a sequestered malformation with no discernable venous drainage to the surrounding venous system. Type 2 has small normal appearing draining veins into the superficial or deep venous system. Type 3 has enlarged and ectatic draining veins. In Type 4, the malformation itself consists of dilated venous ectasia. The presence of ectatic vessels that connect to the deep venous system conveys an increased risk of deep vein thrombosis (DVT) and the sequela of thrombotic emboli including pulmonary embolus (PE). Thrombosis in a Type 1 or 2 lesion is unlikely to cause a DVT or PE compared to the higher risk demonstrated in Type 3 and 4 lesions. MR venography, ultrasonography, and direct venography may be helpful to demonstrate these dangerous connections to the deep venous system. The degree of functional impairment, the severity of pain, and the risk of potential deep embolic VTE are used to determine the need for invasive therapeutic interventions such as sclerotherapy or vessel embolization (12).

A positive D-dimer can be found in 42% of patients with a VM (13). This is close to five times higher than those with other non-venous vascular malformations (14). As a surrogate marker for thrombin activation, the D-dimer already plays a prominent role in the diagnostic work up for suspected thromboembolism in pediatric and adult medicine. However, the D-dimer is uniquely useful to identify a venous component of complex or unclear vascular malformations. Sepulveda et al. carried out one of the few studies focused on pediatric patients with vascular malformations complicated by thrombosis. The authors suggested clinical and laboratory factors associated with higher risk of thrombotic complications include the extent of the malformation, presence of palpable phleboliths, increased age, and elevated D-dimer (15). A child's platelet count can be mildly decreased in LIC, which helps distinguish the LIC of VMs from the severely low platelet counts demonstrated in the Kasabach–Merritt phenomenon (KMP), a coagulopathy specific to the vascular tumors kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) (see Vascular Tumors) (8). The coagulopathy in VMs has been shown to worsen with interventional procedures such as sclerotherapy and embolization, consisting of decreased platelets, a drop in fibrinogen, and the conversion from a negative to positive D-dimer (14).

Complex Combined Vascular Malformation Syndromes

Complex combined vascular malformation syndromes, like Klippel–Trenaunay syndrome (KTS), are associated with an increased frequency of VTE. It is the venous and venolymphatic components of these lesions that demonstrate the increased thrombophilia. The thrombi in these complex combined syndromes range from superficial and minimally symptomatic phleboliths to large vessel life-threatening DVTs and PEs. Blood flow is perturbed and slowed through varying degrees of ectatic vessels that activate the local coagulation system and results in the formation of recurrent thrombi (16).

Klippel–Trenaunay syndrome is a rare congenital vascular malformation syndrome characterized by a combination of capillary, lymphatic, and VMs (CLVM) associated with localized abnormal overgrowth of bone and/or soft tissue that often results in limb hypertrophy. Patients with KTS commonly demonstrate a mild coagulopathy and an elevated D-dimer that develops from extensive clumps of slow-flow malformation. These patients are prone to both bleeding and thrombotic complications. DVTs are life-threatening complications reported to occur in 8–22% of KTS patients (16–18). KTS patients can demonstrate rudimentary deep venous systems with persistent embryonal veins such as the lateral vein of servelle or lateral marginal vein in the affected lower extremity and a persistent sciatic vein (19). These veins predispose to stasis and cannot be removed since the deep system is not developed and removal will place the patient at risk of venous hypertension. Enlarged ectatic veins connected to central veins place the patient at risk of developing PE. A specific incidence of PE is difficult to be reported as the literature consists of case reports and case series (20–22). One study reports an incidence of 4% PE and 4% DVT (23). Chronic thromboembolic pulmonary hypertension results from incomplete resolution of the vascular obstruction caused by PE. It tends to occurs at an older age in patients with KTS or large VMs after a history of recurrent PE (24). To adequately monitor for chronic pulmonary complications, a pediatric pulmonologist should be involved in the multidisciplinary care of KTS patients.

The development of thrombosis occurs at greater frequency post-operatively, post-procedurally, and after trauma. A large cohort of KTS patients studied by Oduber et al. compared children with KTS to young–adult controls and demonstrated higher D-dimer levels ($p < 0.001$) in KTS patients. Additionally, the median levels of protein C ($p = 0.003$) and protein S ($p = 0.01$) were significantly lower in the KTS patients (21). The D-dimer can be used to help differentiate complex combined lesions with predominantly slow-flow VMs from lesions with predominantly fast-flow arteriovenous malformations like Parkes–Weber syndrome (25).

Proteus syndrome is characterized by an asymmetric overgrowth of body parts, vascular malformations, epidermal nevi, and dysregulated adipose tissue. It is associated with mutations in the AKT1 gene and PTEN mutations. Patients with Proteus syndrome carry an increased risk for DVT and PE, likely secondary to stagnant flow in the dilated anomalous veins in the affected limb (26).

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis abnormalities) is part of the PIK3-CA-related overgrowth syndromes. Patients with CLOVES syndrome may have abnormalities in central conduction with central and thoracic phlebectasia that places them at higher risk for PE and sudden death, especially during procedures (27, 28).

VASCULAR TUMORS

Vascular tumors are abnormal proliferations of cells of vascular origin. They are divided between benign hemangiomas (including infantile and congenital), the more aggressive and infiltrating KHE and TA, and a rare category of malignant vascular tumors that includes angiosarcoma (29). Infants with a benign infantile hemangioma (IH) may demonstrate a slightly elevated platelet count, D-dimer, and a slightly lower fibrinogen level. However, these infants neither develop clinically symptomatic coagulopathies or VTE. Congenital hemangiomas, which are histologically distinct from IH, are divided into a rapidly involuting (RICH), non-involuting (NICH), or partially involuting congenital hemangiomas. The RICH subtype may demonstrate a mild coagulopathy consisting of thrombocytopenia, low fibrinogen, elevated D-dimers, and fibrin degradation products. This coagulopathy, however, is typically self-limited and not associated with bleeding complications (30).

Kaposiform hemangioendothelioma is a vascular neoplasm of infancy and childhood that, unlike classic IHs, does not undergo spontaneous involution. It can develop a life-threatening coagulopathy known as the KMP, which includes severe thrombocytopenia, hypofibrinogenemia, and consumptive coagulopathy (31). The cause of this coagulopathy has been theorized to be secondary to trapping and consumption of inappropriately activated platelets combined with hyperfibrinolysis (2). Unlike the thrombosis risk associated with the LIC of venous and venolymphatic malformations, vascular tumors with KMP carry a disproportionate increased risk of severe hemorrhage and is associated with a 10–30% mortality risk (32). Cause of death is often related to hemorrhage, functional impairment, high output cardiac failure, and shock.

THERAPY

There are no established evidence-based guidelines to prevent and treat VTE in children with vascular anomalies. Individual and consensus practice publications have described mostly supportive care measures as there have been no prospective pharmacotherapy trials to address VTE in pediatric vascular anomalies. Multidisciplinary approach is important to proper treatment planning and better outcomes.

Patients with slow-flow vascular malformations (VM, LVM, or CLVM) should undergo evaluation by a pediatric hematologist for baseline screening, peri-operative management, and/or pregnancy planning. Laboratory evaluation, at minimum, should include complete blood cell count, measurement of prothrombin time, activated partial thromboplastin time, plasma D-dimer, and fibrinogen. Guided by clinical suspicion, additional thrombophilia labs to consider include serum protein C and S levels, antithrombin levels, and screening for the prothrombin gene and

Factor V Leiden gene mutations. Patients and families should be provided education on the signs and symptoms of thrombosis and thromboembolic complications. Practitioners caring for patients with high-risk lesions should have a low threshold for diagnostic testing. Patients with extensive slow-flow lesions and complex combined lesions require long-term monitoring for thrombotic complications (12). Patients should be advised to avoid additional prothrombotic risk factors including obesity and the use of estrogen-based oral contraceptives (17).

The use of well-fitted high-quality, elastic compression garments has become a standard of care in most vascular malformations that include a venous component (VM, LVM, CLVM). When used appropriately, the compression garment acts to reduce transmural pressure, prevent venous stasis, limb swelling, and can decrease LIC (7, 8). The result is reduced phlebolith formation and decreased pain. Data to support the benefits of compression garments are primarily extracted from adult studies that demonstrate reduced rates of post thrombotic syndrome in patients with VTE (33).

There has been a long-standing, but poorly studied, role for anticoagulation in the treatment of slow-flow vascular malformations. The strategic administration of low-molecular-weight heparin (LMWH) has been used in attempts to suppress LIC, drive down elevated D-dimers, and essentially "calm down" the over activated coagulopathy and consumption demonstrated in many VMs. Unfortunately, the field has yet to carry out adequate prospective trials to study the efficacy and safety of anticoagulation in this population. Furthermore, the field has yet to develop consensus criteria to guide when anticoagulation use is indicated, what dose should be administered, and how long therapy should continue. Factors commonly evaluated in the decision to initiate anticoagulation include the degree and type of venous ectasia and laboratory evidence of LIC including elevated D-dimer and reduced/consumed fibrinogen.

Common practice is to consider use of LMWH to prevent complications of hemorrhage or thrombosis during and after interventional or surgical procedures and to alleviate the symptoms of pain associated with VM thrombosis. To prevent peri-procedural complications, prophylactically dosed LMWH (0.5 mg/kg/dose once or twice a day subcutaneously) is often administered for at least 2 weeks prior to a procedure and is continued for an additional 2 weeks post-procedure (34). Short courses (2–3 weeks) of prophylactically dosed LMWH are often administered to alleviate the pain caused by inflammation and thrombosis/phleboliths occurring within extensive VMs. Depending on phlebolith location, they can be quite painful and greatly impact a child's quality of life. Even when prophylactically dosed, poor drug clearance is theoretically possible in extensive malformations and it remains undetermined if and how often serum LMWH anti-Xa levels should be monitored. Patients that receive prolonged exposure to LMWH should have blood counts checked routinely and a bone densitometry (DEXA) scan should be completed to evaluate for ongoing osteopenia. Temporary IVC filter placement may be necessary in patients with high risk for DVT/PE such as CLOVES or KTS (22, 28).

There is equivocal evidence to support the use of antiplatelet agents to reduce LIC in patients with VMs. The LIC in slow-flow lesions is based on the consumption of coagulation factors and does not result in either a significantly decreased or increased platelet count. Therefore, without any prospective trials to guide safety and efficacy, providers anecdotally use aspirin and non-steroidal anti-inflammatory (NSAIDS) agents to stabilize symptoms, reduce inflammation, and decrease severity of pain episodes (35).

For children with symptomatic lesions that cause pain and/or deformity, sclerotherapy is a first-line intervention to consider. Treatment involves percutaneous, catheter-directed injection of a sclerosant such as dehydrated alcohol (ethanol) or sodium tetradecyl sulfate (Sotradecol). Injecting one of these irritants induces endothelial damage and encourages the malformed vessel to scar down on itself. Immediately after a sclerotherapy procedure, fibrinogen and platelet levels decline and D-dimer elevates higher than normal values (14). For lesions at high risk for VTE, several techniques have been described to block the draining veins, allow the sclerosant to remain in the malformation, and reduce the risk of off-target vessel exposure. Endovenous laser or radiofrequency ablation of the draining veins has been described. An additional interventional approach to block draining veins is embolization with coils, *n*-butyl-2-cyanoacrylate liquid emboli (nBCA) or onxy (36, 37). There is scant new data to support the use of cryoablation techniques for the treatment of large symptomatic VMs (38).

Surgery is also considered as a first-line therapy for the treatment of symptomatic VMs. When appropriate, surgery aims at total resection of the malformation to decrease negative impact of the lesion and decrease risk of recurrence. However, given the potential for hemorrhagic complications in extensive, ectatic VMs, surgical debulking is not always possible or only possible with adjunct sclerotherapy or nBCA/onxy embolization. Patients with underlying LIC are at risk to develop peri-operative DIC and, if the underlying lesion is not completely excised, there is an increased risk of post-operative hemorrhage. Rapid administration of blood replacement products (including fresh frozen plasma, cryoprecipitate) and antifibrinolytic agents may be indicated to stop post-operative hemorrhagic complications (39).

CONCLUSION

The development of VTE in pediatric vascular anomalies greatly impacts a patient's quality of life and influences therapeutic decisions. Early screening of high risk lesions is recommended and evaluation may include imaging, laboratory testing, and appropriate documentation of any functional impact the lesion has. With an increased awareness of the pathophysiology and clinical impact of VTE in vascular malformations, prospective trials and consensus pediatric guidelines are necessary for the field to standardize care and to determine the safety and efficacy of pharmacotherapy interventions. A multidisciplinary approach is vital to the proper management of pediatric vascular anomalies to ensure all surgical, interventional, pharmacological, and supportive care options have been considered.

AUTHOR CONTRIBUTIONS

TN and CZ both contributed, designed, and wrote the manuscript.

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Risk Factors, Prophylaxis, and Treatment of Venous Thromboembolism in Congenital Heart Disease Patients

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Congenital heart disease (CHD) is a common condition in the pediatric population, affecting up to 1% of all live births (i.e., around 40,000 newborns/year in the United States). Although CHD does have a wide range of severity, by the age of 5 years approximately 80% of patients will require at least one surgical intervention to achieve a complete/palliative cardiac repair. Today, in light of their much-improved surgical survival, the care of these patients focuses on morbidity prevention and/or treatment. One such morbidity has been the increased frequency of thrombotic occlusions [e.g., cardioembolic arterial ischemic strokes; arterial, cardiac, and/or newly created shunt thrombosis; venous thromboembolism (VTE)]. Patients with CHD are at high risk of developing thrombosis due to the disruption of blood flow, CHD-related coagulopathy, inflammation, and/or platelet activation secondary to extracorporeal circulation support required during open-heart surgery or as a bridge to recovery, which can increase thrombus formation. In this article, we will discuss how the coagulation system is altered in patients with CHD in regard to the patient's anatomy, procedures they undergo to correct their congenital heart defect, and other risk factors that may increase their thrombotic risk, focusing on VTE. We will also discuss the most recently published reports pertaining to guidelines on prophylaxis and treatment of VTE in this population. Finally, we will briefly address the long-term VTE outcomes for patients with CHD.

Keywords: congenital heart disease, venous thromboembolism, venous thromboembolism prophylaxis, venous thromboembolism treatment, congenital heart disease and thrombosis, venous thromboembolism risk factors

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INTRODUCTION

Congenital heart disease (CHD) is a common condition that affects approximately 40,000 births/year in the United States. Most cardiac birth defects classified as CHD occur in healthy children and are relatively minor (1). By contrast, until recently, complex CHD was accompanied by a significant mortality rate. Although survival has significantly improved, CHD patients are still at risk of significant morbidities particularly after their cardiac surgeries (2). Therefore, a better understanding of venous thromboembolism (VTE), one of the most common types of thrombotic occlusions occurring in this specific group, has become imperative, due to the increasing VTE incidence in hospitalized pediatric patients, including CHD patients (3–5). Moreover, it is well known that CHD is one of the main underlying conditions contributing to VTE in pediatric patients (6, 7).

Congenital heart disease patients are at high risk of developing thrombosis for various reasons: the type of cardiac defect, CHD-related complications, and stage of their care. For example, many of the structural cardiac abnormalities lead to changes in blood rheology or to natural anticoagulant deficiencies due to hepatic hypoperfusion secondary to impaired heart function, further contributing to a hypercoagulable state. In addition, many patients undergoing open-heart surgery necessitate cardiopulmonary bypass, where the required blood product exposure can lead to hemodilution and coagulation derangements. Finally, the increasing use of central venous catheterization in the care of such patients has also contributed to the VTE incidence escalation in this patient population.

This review will discuss several factors that increase the risk of developing thrombosis in CHD patients, including coagulation system changes due to their CHD and the procedures that they undergo to correct their heart defects. VTE prophylaxis and treatment will also be discussed. As these patients now have a normal or near normal lifespan, long-term VTE outcomes will also be discussed briefly.

DIFFERENCES IN THE COAGULATION SYSTEM OF CHD PATIENTS

The coagulation system in neonates and infants is physiologically distinct from adulthood. Neonates and infants have lower concentrations of both pro-coagulant and natural anticoagulant proteins compared to adult values, as a reflection of the physiologic developmental hemostasis process that occurs in all children. Circulating levels can take up to 12 months, and in some instances only reach adult levels in adolescence (8, 9). Furthermore, neonatal and infant CHD patients have lower concentrations of pro-coagulant and natural anticoagulant proteins than normal age-appropriate controls (10–13). The cause for lower concentrations of coagulation proteins is believed to be multifactorial (i.e., increased consumption, decreased production, and increased fibrinolysis).

As CHD patients have their surgical corrective procedures, the coagulation profile showing decreased pro-coagulant and anticoagulation proteins is enforced. Odegard et al. examined coagulation profiles of 37 patients with hypoplastic left heart syndrome before their stage I palliation, bidirectional Glenn, and before and after the Fontan procedure. The investigators found that all coagulation proteins were at significantly lower concentrations except for factor VIII, which only increased after the Fontan procedure (12). The authors posited that the increased factor VIII production was due to increased production from liver sinusoidal epithelium secondary to chronically elevated central and hepatic venous pressures associated with Fontan physiology.

Congenital heart disease patients may also present with thrombocytopenia (10), which is multifactorial. For instance, thrombocytopenia can be secondary to hypoxic inhibition of platelet production, increased platelet destruction with shunt placement in single-ventricle physiology, or increased RBC production. Lill et al. hypothesized that right-to-left shunts in CHD patients decreased megakaryocyte delivery to the lungs, impairing platelet production in the pulmonary bed (14). In addition, CHD patients have been shown to have abnormal platelet function. Maurer et al. reported decreased aggregation when platelets were exposed to platelet agonists (15). Furthermore, Bailly et al. found patients with systolic flow abnormalities to have abnormal platelet function (16), which could be explained by the fact that CHD patients may develop acquired von Willebrand disease, known to affect platelet aggregation testing (17). Finally, CHD associated with other genetic disorders may also present with platelet dysfunction. CHD patients with Noonan's syndrome, velocardiofacial syndrome, and Jacobson's syndrome can have quantitative or qualitative platelet defects, which can increase risk of bleeding.

THE COAGULATION SYSTEM AND CARDIOPULMONARY BYPASS (CPB)

Patients who undergo CPB are temporarily exposed to a non-physiologic circulatory system, which disrupts their coagulation system. Once CPB is initiated, the contact factors are activated, and tissue factor is exposed, which lead to increased thrombin generation. Upon thrombin generation, production of fibrin as well as protein C activation (18) ensues. Therefore, as a result of the increased thrombin generation and subsequent fibrin deposition within the CPB circuit, anticoagulation is required during CPB to prevent excessive thrombus formation. In addition to consumption of several coagulation factors within the circuit, platelets are significantly affected during CPB. When CHD patients are placed on CPB, platelet activation occurs immediately (19, 20) followed by platelet consumption, leading to an acquired quantitative or qualitative platelet defect (21). Patients younger than 1 year of age are more likely to have this complication. Second, hemodilution due to priming of the CPB circuit can also lead to thrombocytopenia. Third, CPB confers a pro-inflammatory state as it activates both humoral and cellular aspects of the immune system (18). With the activation of the inflammatory response, endothelial cells will express tissue factor, further promoting thrombin generation (22). Consequently, in light of the CPB-induced coagulopathy that may develop, CHD patients have an increased risk of bleeding in the immediate post-operative period and can be treated with blood-derived products, anti-fibrinolytics, and hemostatic agents such as recombinant activated factor VII (23), as needed.

CYANOTIC CHD AND THROMBOSIS RISK FACTORS

Patients with cyanotic CHD (e.g., Tetralogy of Fallot, tricuspid atresia, and single-ventricle physiology) can be at high risk of developing VTE due to the surgical procedures required to correct their originally abnormal cardiac anatomy. The Blalock–Taussig (BT) shunt is a common surgical procedure in neonates with single-ventricle physiology, where a shunt is created between the subclavian artery and the ipsilateral pulmonary artery to increase pulmonary blood flow (24, 25). This shunt creates a low blood flow area that increases the risk of thrombosis, and surgically removed shunts have been found to be obstructed. Of note, complete BT

shunt obstruction creates a significant decrease in pulmonary blood flow, almost invariably requiring an immediate mechanical thrombectomy. The frequency of BT shunt thrombosis reported in the literature ranges from 1 to 17% (24). Wells et al. reported BT shunt histopathology for the detection of shunt obstruction from 155 patients and found a median shunt lumen narrowing of 34%. Moreover, 21% of cases showed a shunt stenosis greater than 50%. The identified risk factors for obstruction were smaller shunt size, age less than 14 days, and shunt placement while on bypass (26).

A second palliative surgical procedure to increase oxygenation in patients with single-ventricle physiology is the bidirectional Glenn procedure. This procedure connects the superior vena cava to the right pulmonary artery (27). The largest concern regarding thrombosis is the development of pulmonary embolism, with a subsequent increase in pulmonary vascular resistance, making patients unsuitable for further palliative surgeries (25). Though Glenn Shunt thrombosis is rare, a study by Manlhiot et al. comprising 203 cardiac operations performed in single-ventricle patients showed that the second highest occurrence of VTE (12%) corresponded to cavopulmonary shunt operations (28).

The final palliative surgical stage for single-ventricle physiology patients is the Fontan procedure. This procedure involves rerouting the systemic venous return directly to the pulmonary arteries (29). The Fontan procedure has undergone many modifications, though the mechanism of the anastomosis of the inferior vena cava to the pulmonary arteries has remained unchanged (25). Patients undergoing the Fontan procedure are also at an increased risk of developing thromboembolism, and the reported incidence of thromboembolism ranges from 3 to 20% (30). Identified post-Fontan thrombosis risk factors include passive blood flow, chronic venous hypertension, and atrial arrhythmias. Patients undergoing Fontan procedures were found to have elevated factor VIII levels, which may further increase VTE risk (12). Patients may or may not have a fenestration placed within the atria; the latter procedure could lead to the development of paradoxical emboli if a thrombotic source is present within the right cardiac chambers. As many modifications have been made to the Fontan, Coon et al. examined whether thrombosis rates and risk factors varied among patients undergoing different types of procedures. No difference was found in thrombosis incidence in either the pulmonary or venous system in any of the modifications (31). These findings suggest that the physiology of the Fontan circulation leads to thrombus formation.

Additional cyanotic CHD conditions do not pose higher thrombotic risk. The higher risk of these patients developing thrombosis is more strongly associated with CPB and the coagulation abnormalities described earlier.

ACYANOTIC CHD

Patients with acyanotic congenital heart lesions do not usually have a significant rate of thrombotic complications. Depending on the type of atrial/ventricular septal defect, the patient may or may not undergo CPB surgery to close the defect (32). Ventricular septal defects are more likely to require surgical closure than atrial septal defects. Recent advances in interventional closure devices, specifically for perimembranous ventricular septal defects, have decreased the need for CPB (33, 34).

CARDIAC CATHETERIZATION

Congenital heart disease patients commonly undergo a cardiac catheterization procedure for both diagnostic and treatment purposes. When undergoing cardiac catheterization, the femoral artery or femoral vein is accessed for catheter insertion immediately prior to a bolus of unfractionated heparin (UFH). Thrombosis and pulse loss after catheterization are known complications of this procedure. Venous thrombosis has a prevalence ranging from 0 to 27% and the reported prevalence for femoral artery occlusion is between 0.6 and 9.6% (35–38). Post-cath thrombosis risk factors in both the femoral artery and vein include younger age, patient size, use of larger catheters, longer procedural time, and need for repeat procedures.

VTE PROPHYLAXIS FOR CHD PATIENTS

Due to the high risk of developing thrombosis with CHD and cardiac surgery, studies have examined the role of thromboprophylaxis to decrease thrombosis development. Low molecular weight heparin (LMWH), oral vitamin K antagonists (OVKA; i.e., warfarin), and aspirin have been successfully used as primary thromboprophylaxis options for CHD patients undergoing cardiac procedures; this strategy has also decreased patient mortality (39, 40). To help clinicians decide which prophylaxis is more appropriate, evidence-based guidelines for the management of CHD patients after cardiac surgery have been published (41–43).

Antiplatelet Therapy

Aspirin is widely used; commonly, it is typically started on patients after systemic to pulmonary shunt placement as long-term prophylaxis. Additionally, aspirin may also be considered for primary prophylaxis in children undergoing the Fontan procedure (44). The usual aspirin dosing for prophylaxis is 3–5 mg/kg daily, and treatment duration can vary. Aspirin prophylaxis may be used in patients undergoing cardiac catheterization if a device is placed during the procedure. Clopidogrel, another antiplatelet agent, is increasingly being used in children (45). Despite its widespread use, a recent trial showed clopidogrel was not more effective than placebo in reducing mortality or shunt-related morbidity in high risk CHD patients (46).

Anticoagulation Therapy

Unfractionated heparin and warfarin are the most commonly used anticoagulants for patients undergoing cardiac surgery. UFH is used mostly as an immediate post-operative medication for thromboprophylaxis, particularly in patients undergoing a systemic to pulmonary shunt placement. For patients with clinically significant post-operative bleeding, low-dose standard heparin may be preferred prior to starting antiplatelet therapy. Systemic heparinization may also be continued with additional antiplatelet therapy if there is sustained high risk of developing thrombosis. In such cases, further evaluation regarding the

thrombosis risk will determine whether the UFH infusion needs to be switched to LMWH in addition to aspirin.

Warfarin prophylaxis may be started on patients after the Fontan procedure for, at least, 3–12 months. Warfarin may be continued for much longer periods when in the presence of certain thrombosis risk factors. Patients are usually dosed to maintain an international normalized ratio (INR) between 2.0 and 3.0 to minimize bleeding risk. Point-of-care monitoring is likely an option for outpatient INR laboratory monitoring in children receiving long-term oral anticoagulation with an OVKA (47). Direct oral anticoagulants (DOACs) are not approved for use in the pediatric population and are only recommended for pediatric patients if they are participating in a clinical trial. At present, there is only one clinical trial open for the use of a DOAC in CHD patients (Apixaban in Children with Cardiac Conditions; NCT02981472).

Patients undergoing a cardiac catheterization usually receive a heparin bolus prior to and possibly during the catheterization, if the procedure extends beyond 2 h. Patients are usually given 100 U/kg prior to the procedure, but smaller doses have also been employed (48). Activated clotting time allows monitoring monitor anticoagulation, and heparin bolus dosing should be determined following the American Heart Association Guidelines (43).

RISK FACTORS OF VTE IN CHD PATIENTS

Besides cardiac procedures, additional thrombosis risk factors have been identified in CHD patients (**Table 1**). Likely, the most pervasive VTE risk factor in children is central line (CVC) use. Central venous access is vital to manage children post-operatively, and many children with CHD will have multiple CVCs placed at once in both the lower and upper extremities. Moore et al. prospectively evaluated CVC-related VTE in CHD patients *via* lineograms at CVC removal and reported a VTE prevalence of 20%. All lines were placed in the jugular veins; 60% of thromboses were located in the jugular veins while the remaining 40% were located in the right atrium (49). Additionally, Hanson et al. found 41% of CHD patients developing a VTE to have a CVC-related event. The time length of CVC placement was directly associated with thrombosis (50).

Other studies have examined additional potential VTE risk predictors, including clinical and laboratory markers. Tzanetos et al. examined 19 patients who underwent palliative surgery for single-ventricle physiology and found that those who developed thrombus had worse pre-operative ventricular function, longer CPB time, decreased circulating antithrombin levels, and increased tissue plasminogen activator antigen concentrations (55). Similarly, Petaja et al. examined 10 neonates who underwent CPB. Three patients developed thrombosis and were found to have decreased circulating antithrombin or protein C levels and elevated plasminogen activator inhibitor levels (63).

Aspirin prophylaxis response has also been explored as a predictor of VTE development. Emani et al. described decreased aspirin response as a predictor for VTE development; 95 patients were followed 30 days after initiation of aspirin therapy. Patients not responding to aspirin, particularly patients weighing less than 5 kg had a higher thrombosis rate compared to those showing adequate aspirin response (53). Mir et al. examined the incidence of aspirin responsiveness in 20 infants with single-ventricle physiology after palliative heart surgery by measuring urine thromboxane (UTX) levels and thromboelastography (TEG). The authors found aspirin resistance in around 80% of infants using TEG; no patients had adequate UTX levels and clinical variables such as age, weight, hemoglobin level, and platelet count were not associated with aspirin resistant status (66).

Congenital heart disease patients who undergo cardiac surgery are also at risk for developing ischemic stroke. Domi et al. examined 5,526 patients who underwent cardiac surgery and found that the incidence of arterial ischemic stroke/cerebral sinus venous thrombosis was 5.4 strokes per 1,000 children. Risk factors associated with stroke included older age, longer duration of CPB, reoperation, and number of days hospitalized after the operation (67).

VTE TREATMENT FOR CHD PATIENTS

Patients with an acute, symptomatic VTE and no relevant contraindication are treated with anticoagulation, namely, systemic UFH or LMWH (41–43). The anticoagulation modality of choice depends on the circumstances of the patient (surgical needs, liver/kidney dysfunction). Patients started on systemic anticoagulation for VTE are usually treated for 3–6 months (41–43). Moreover, patients receiving systemic anticoagulation should be monitored throughout treatment for bleeding complications, and frequent laboratory testing is recommended to ensure their anticoagulation dosing is therapeutic. For patients undergoing UFH therapy, a target PTT of 70–100 s, which correlates to an anti-factor Xa level of 0.3–0.7, is considered therapeutic. For patients undergoing LMWH therapy, an anti-factor Xa level of 0.5–1.0 is considered therapeutic. Patients may be transitioned to warfarin therapy depending on their clinical circumstances, and the target INR for these patients is 2.0–3.0. If the patient does have a life or limb-threatening thrombus, thrombolysis should be strongly considered (41–43).

OUTCOMES FOR CHD PATIENTS WITH VTE

Patients who undergo CPB surgery can be at significant risk of developing comorbidities if they develop VTE (**Table 1**). Manlhiot et al. retrospectively reviewed 1,361 CHD patients after cardiac surgery and described morbidities associated with VTE. VTE was associated with increased number of ICU days and increased length of stay. VTE was also associated with increased risk of cardiac arrest, and thrombosis-related mortality was 5%. However, in light of the retrospective study design, VTE causality could not be inferred (5). Pejata et al. also conducted a single center retrospective review to evaluate mortality in 20 CHD patients after developing thrombosis. VTE was associated with increased mortality rate, as VTE patients

TABLE 1 | Published literature regarding thrombosis risk factors and outcomes in CHD patients.

Reference	Study design	Prospective/ retrospective	Number of patients	Main VTE findings	Limitations
Faraoni (51)	Database review of CHD patients	Retrospective	27,492	Thrombotic complications in 3.9% of surgical CHD patients; younger age, single-ventricle physiology associated with increased risk	Retrospective; no access to pt charts, data could be missed or miscoded, causality not established
Manlhiot et al. (28)	Cohort of CHD patients who developed thrombosis and outcomes	Retrospective	192	Serious complications occurred with 17–24% of thrombi, 13% of patients had bleeding complications	Retrospective, no standardized follow-up, unable to assess for thrombophilia, asymptomatic thrombus not identified
Jensen et al. (52)	Cross-sectional study examining pulmonary and cerebral thrombosis	Prospective	98	Prevalence of cerebral and pulmonary thrombosis: 47 and 31%	Unable to determine when the thrombotic event occurred, small sample size
Emani et al. (53)	Single-ventricle physiology cohort	Retrospective	512	51 patients developed thrombosis (10%); patients with thrombosis had longer ICU and hospital stays, single-ventricle physiology and CBP were risk factors	Retrospective, small number of patients, small number of thrombotic events
Wessel et al. (46)	Multicenter, randomized double-blind, placebo controlled study examining clopidogrel in CHD patients	Prospective	906	Clopidogrel did not reduce mortality or shunt-related morbidity	Heterogeneity of the patient population, could not compare Aspirin + clopidogrel vs. clopidogrel alone, difficulty to diagnose shunt thrombosis
Idorn (54)	Population-based study of Fontan patients	Retrospective for prevalence, prospective for laboratory testing	210	Thromboembolic prevalence was 8.1%, no evidence of hypercoagulability in the patient groups	Blood samples not taken at the time of thrombotic event, could not establish reference ranges for coagulation tests
Manlhiot (39)	Cross-sectional study of patients undergoing cardiac surgery	Retrospective	357	Thrombotic incidence was 40 and 28% after initial palliation and superior cavopulmonary connection, thromboprophylaxis with enoxaparin was associated with a reduced risk of thrombotic complications, thrombosis was associated with increased mortality	Retrospective, no control group
Hanson et al. (50)	Observational study for VTE risk factors in critically ill CHD patients	Prospective	1,070	VTE incidence was 3.8% with 37% of VTEs being CVC-related; VTE was associated with single-ventricle physiology, and more CVC days	Heterogeneity of the patient population, no screening of VTE
Tzanetos et al. (55)	Observational study for predictors of thrombosis in single-ventricle physiology patients	Prospective	16	Perioperative thrombus incidence was 31%, thrombus associated with longer CPB times, poor ventricular function, and lower antithrombin and tissue plasminogen activator antigen levels	Small sample size, no control group, no long-term follow-up data, unequal distribution of patients among surgical intervention groups
Monagle et al. (44)	Multicenter, randomized trial comparing ASA vs. heparin/warfarin for primary prophylaxis	Prospective	111	No difference between the ASA vs. heparin/warfarin arms	Poor recruitment leading to less than optimal number of patients
Manlhiot et al. (5)	Single center, cohort study of CHD patients	Retrospective	1,361	VTE incidence was 11%, VTE associated with increased number of ICU and hospital days, cardiac arrest, and higher mortality	Retrospective, possible incomplete medical records, unable to prove causality between VTE and morbidity/mortality
Kim (56)	Cohort study of CHD patients	Retrospective	200	VTE occurred in 13 patients (6.5%), mostly happening within 1 year after the Fontan procedure	Retrospective, small sample size
Hanslik (57)	Cohort study of CHD patients	Prospective	90	VTE was detected in 25 patients (28%), all VTEs occurred in the right jugular vein	Possible overestimation of sensitivity of diagnostic tests, follow-up monitoring not done
Li et al. (40)	Multicenter non-randomized, observational study examining aspirin efficacy in lowering risk of death and shunt thrombosis	Prospective	1,004	Patients on ASA with lower risk of shunt thrombosis and death	Non-randomized, observational, no other antiplatelet or anticoagulation given, shunt characteristics not related to shunt thrombosis
Cholette (58)	Observational study of neonates undergoing cardiac surgery	Prospective	22	5/22 (23%) patients had evidence of thrombosis, C-RP elevation was the only predictor of thrombosis development	Small sample size

(*Continued*)

TABLE 1 | Continued

Reference	Study design	Prospective/ retrospective	Number of patients	Main VTE findings	Limitations
Kaulitz (59)	Cohort of patients undergoing total cavopulmonary anastomosis	Retrospective	142	10 patients (7%) suffered thrombotic events, 8 patients with VTE, and 2 patients with stroke	Retrospective, small number of patients
Gurgey (60)	Review of CHD patients with thrombosis and thrombophilic factors	Retrospective	28	Overall frequency of Factor V Leiden and prothrombin Gene mutation was 22%, 5 patients had the FVL gene mutation and 1 pt had the prothrombin gene mutation	Retrospective, no control group, small sample size
Seipelt (61)	Cohort study of CHD patients	Retrospective	101	Thrombotic events happened in 13/85 hospital survivors (15.3%)	Retrospective, small number of patients
Jacobs (62)	Survey of patients who underwent Fontan procedure and aspirin use	Retrospective	72	No thrombotic event was documented (0%)	Retrospective, no control group, small number of patients
Coon et al. (31)	Echocardiogram findings in Fontan patients	Retrospective	592	Thrombosis prevalence 8.8%	Retrospective, various time intervals until imaging was performed
Petaja et al. (63, 64)	Single center, cohort study of CHD patients	Retrospective	1,499	Central venous thrombosis incidence was 1.1%; mortality associated with central venous thrombosis was 40%	Retrospective
Petaja et al. (63, 64)	Single center cohort study of CHD patients	Retrospective	10	3 patients who developed thrombosis had decreased antithrombin or protein C levels and elevated plasminogen activator inhibitor levels	Retrospective, small sample size
Rosenthal (65)	Cohort study of patients undergoing the Fontan procedure	Retrospective	70	14 patients (20%) developed thromboembolism with 12/14 thrombi located in the venous circulation	Retrospective, small number of patients

CHD, congenital heart disease; VTE, venous thromboembolism; ASA, aspirin; ICU, intensive care unit; CPB, cardiopulmonary bypass; C-RP, C-reactive protein; CVC, central venous catheter.

had a 40% mortality rate compared to patients who did not develop VTE (8.3%). Again, due to the study limitations, causality between VTE and mortality could not be established (64).

LONG-TERM OUTCOMES FOR CHD PATIENTS

Post-thrombotic syndrome (PTS; chronic venous insufficiency secondary to vessel damage) is recognized as an important long-term complication in CHD patients. Brandao et al. examined 70 CHD patients aged 0.5–5 years after their surgical repair and found that 30% of patients had clinical evidence of PTS (68). Most patients had lower limb PTS, and all patients had mild PTS.

Post-thrombotic syndrome after cardiac catheterization is a newly recognized long-term complication for patients. Luceri et al. studied 62 patients who underwent cardiac catheterization and found that 40 children had PTS (prevalence 64%, 95% CI 51.3–76.3%). Most cases were mild, though seven children had clinically significant PTS (69).

Importantly, CHD patients seem to carry their increased thrombotic risk into adulthood. Jensen et al. reported a prevalence of cerebral and pulmonary thrombosis of 47 and 31%, respectively, in adult survivors (52).

CONCLUSION

The risk of thrombosis development in CHD patients is multifactorial. Thrombotic events lead to short- and long-term complications for these patients. Although guidelines for thromboprophylaxis and treatment are currently available, more research is needed to increase the knowledge of how thrombosis develops in these patients and how to prevent this common complication.

AUTHOR CONTRIBUTIONS

MS performed the literature search and wrote the manuscript. LB also performed the literature search and edited the manuscript.

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Pediatric Hospital Acquired Venous Thromboembolism

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Pediatric hospital acquired venous thromboembolism (HA-VTE) is an increasing problem with an estimated increase from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to a current estimate of 30–58 events per 10,000 pediatric hospital admissions. Pediatric HA-VTE is associated with significant morbidity and mortality. The etiology is multifactorial but central venous catheters remain the predominant risk factor. Additional HA-VTE risk factors include both acquired (recent surgery, immobility, inflammation, and critical illness) and inherited risk factors. Questions remain regarding the most effective method to assess for HA-VTE risk in hospitalized pediatric patients and what preventative strategies should be implemented. While several risk-assessment models have been published in pediatric patients, these studies have limited power due to small sample size and require prospective validation. Potential thromboprophylactic measures include mechanical and pharmacologic methods both of which have associated harms, the most significant of which is bleeding from anticoagulation. Standard anticoagulation options in pediatric patients currently include unfractionated heparin, low molecular weight heparin, or warfarin all of which pose a monitoring burden. Ongoing pediatric studies with direct oral anticoagulants could potentially revolutionize the prevention and treatment of pediatric thrombosis with the possibility of a convenient route of administration and no requirement for monitoring. Further studies assessing clinical outcomes of venous thromboembolism (VTE) prevention strategies are critical to evaluate the effectiveness and harm of prophylactic interventions in children. Despite HA-VTE prevention efforts, thrombotic events can still occur, and it is important that clinicians have a high clinical suspicion to ensure prompt diagnosis and treatment to prevent further associated harms.

Keywords: pediatric, venous thromboembolism, hospital acquired, prevention, central venous catheter

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EPIDEMIOLOGY

Hospital acquired venous thromboembolism (HA-VTE) is currently considered the second most common contributor to harm in hospitalized pediatric patients secondary only to central line-associated infection (1). It is a rapidly increasing problem, with an estimated increase from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to a current estimate of 30–58 events per 10,000 pediatric hospital admissions (2–5). The pathogenesis of venous thromboembolism (VTE) is associated with the three main elements described in Virchow's triad, including stasis of blood flow, endothelial injury, and hypercoagulability, and commonly arises as a result of concurrent risk

factors. While the pathogenesis of VTE in pediatric patients is multifactorial, the presence of a central venous catheter (CVC) remains the single most important risk factor (3, 6, 7).

The age of onset for pediatric VTE is bimodal, revealing peaks in the neonatal and adolescent age groups (2). The overall frequency of VTE in the adult population (inpatient and outpatient setting) remains significantly more common than children with an incidence as high as 1 in 100 individuals older than 80 years versus 1 in 100,000 pediatric patients (8, 9). VTE in hospitalized adult patients remains a significant cause of morbidity and mortality and concerted efforts have been made to identify VTE risk factors and to develop effective prevention strategies (10, 11). While less frequent, VTE in hospitalized children also has been recognized as major contributor to harm and effective interventions are needed (1).

The resultant harms in pediatric patients from VTE are numerous and range from death to pulmonary embolism, paradoxical emboli, infection, post thrombotic syndrome, loss of venous access, and pain at the site of thrombosis. Pediatric HA-VTE has been associated with increased length of stay and cost (12). The estimated mortality rate associated with pediatric VTE is 2.2% (6).

RISK FACTORS FOR HA-VTE

Observational, case–control and non-case–control studies in both adults and children have identified a number of VTE risks in hospitalized patients (13). These risks may be either acquired (such as surgery, immobility, inflammatory conditions, CVCs) or inherited (such as Factor V Leiden, prothrombin gene mutation, anticoagulant deficiency). In general, most pediatric patients with a HA-VTE have multiple VTE risk factors present at the time of the thrombotic event.

Recently, Mahajerin et al. performed a meta-analysis of the published studies for VTE risk factors in hospitalized pediatric patients. The authors found that the presence of central catheters, increased length of stay, intubation, and ICU admissions were significantly associated with increased odds ratios for HA-VTE (13). The relative paucity of studies in pediatric patients highlights the challenges of obtaining high quality evidence for this rare event and warrants further research and multi-institutional trials. While a number of studies have demonstrated specific medical conditions, surgical interventions and age as risks for HA-VTE, the low incidence of HA-VTE in children has reduced the power of these studies to detect other potentially relevant clinical risks. We review the current evidence for HA-VTE risks below.

Age

As previously mentioned, the overall incidence of VTE in children is bimodal; there is a peak in infants with subsequent decline in infancy and childhood. The incidence then increases in adolescence and continues to increase throughout adulthood (2, 5, 14). In adults the incidence continues to rise with age and is 10 to 100 times higher than in children (9). The progressive increase in VTE that starts in early adolescence is likely multifactorial. Physiologic changes such as increased FVIII and von Willebrand activity may contribute to increased risk in adults, as well as the use of estrogens in females. In addition, the higher VTE incidence may also reflect the increase in comorbid conditions, such as renal disease, malignancy, and trauma, which are more common in adults (4, 5). Conversely, neonates have a high rate of HA-VTE but this is most likely in large part secondary to the use of CVC's in this critically-ill population, as the rate of CVC-associated VTE is increased in this age group (5).

Mobility

Reduced mobility as a VTE risk factor is well established in the adult population, and some studies in children have also demonstrated this risk (13). However, the details of degree and chronicity of immobility in these studies are not reported. In adult studies, definitions vary considerably (15); some have used bed rest or out of bed for <30 min per day (16). Acute flaccid paralysis has been shown to be a major risk factor for the development of VTE in adults (17). The VTE risk of chronic immobility in children with quadriplegia is less clear. Additionally, the notion that venous stasis is a VTE risk factor in an infant who is not walking is doubtful. Likely, the combination of acute immobility in a hospitalized adolescent patient is a VTE risk, similar to what is seen in adults. A study by Branchford et al. demonstrated that intubation is a risk for HA-VTE, which may be a surrogate for immobility (18).

Medical Conditions

A number of chronic diseases have an increased incidence of VTE, including active malignancy, congenital cardiac disease, renal disease, and rheumatologic disorders (2, 5, 14). Besides the frequent presence of CVCs in patients with these diagnoses, common contributor for VTE risk include acute inflammation, which can result in increases in prothrombotic factors, such a FVIII, vWF, and fibrinogen. Several studies have shown that systemic infection is also a significant VTE risk factor; the mechanisms by which infection contributes to thrombosis are multifactorial (18–20). Infection can be associated with upregulation of prothrombotic factors; in addition, structures called neutrophil extracellular traps can be formed in response to infection and inflammation and are implicated in thrombogenesis (21). Acquired thrombophilia may contribute to risk in hospitalized patients, such as acquired antithrombin deficiency with nephrotic syndrome, a draining chylous effusion or with asparaginase therapy for leukemia. Additional risk factors for HA-VTE in children include obesity and estrogens (18, 22). Overall, medical complexity is a risk as those diagnosed with multiple diseases have an increased odd of VTE (5, 18).

Surgery, Trauma, and Intensive Care

Surgery is a known risk for VTE; this is likely secondary to a combination of factors including a post-surgical inflammatory state, immobility, and CVCs. In particular, some procedures, such as orthopedic surgery is associated with significant risk in adults. However, the incidence of VTE in children with orthopedic procedure appears to be significantly lower for unclear reasons (23, 24). For patients undergoing cardiac surgery, the overall prevalence of thrombosis is significant at 11% (25) with

catheter-associated thrombi in the order of 15% (26). The high VTE rate in these patients may be contributed by stasis and turbulent blood flow associated with congenital heart disease, and by platelet activation with the cardiac bypass circuit. Pediatric trauma patients are also at increased risk; VTE has been shown to be associated with an increased injury severity score, surgery, and blood transfusion (27, 28). There is a significantly higher incidence and risk of VTE in pediatric patients admitted to intensive care units. This finding likely reflects the medical complexity of these patients as well as the other associated risk of CVCs and surgery in this population (13).

Catheters

Central venous catheters are the most common risk associated with VTE in children. The characteristic of CVC placement include location (upper versus lower extremity), type [peripherally placed catheters (PICC) versus implanted], duration, and catheter size. Based on current data, it is unclear if the incidence of VTE with PICCs is greater than with tunneled catheters and prospective studies are needed (29, 30). In surveillance studies, the incidence of VTE associated CVCs placed in the PICU is significant, and has been reported to be 18% (31). While CVC's are more frequently placed in the intensive care units, it is a risk factor in non-ICU settings as well (5, 19, 20). A major problem with catheter-related thrombosis in children is with the size of catheters compared to vessel size. An optimal diameter ratio of 1:3 has been suggested; however, this may not be achievable in infants and small children (32). These physical restraints add to the challenge of VTE prevention with CVCs in this population.

Inherited Thrombophilia

The presence of an inherited thrombophilia, such as a deficiency of antithrombin, protein C or S, or the Factor V Leiden and prothrombin mutations, is associated with an increased odds of developing VTE (33). The odds of VTE are further increased with greater than two genetic traits suggesting that risks are additive. The presence of thrombophilia has been used in risk-assessment models (RAMs) in adults (10) as well as pediatric acute leukemia (34). However, its utility for predicting HA-VTE in the pediatric population has not yet been demonstrated.

VTE RISK ASSESSMENT

With recent incidence estimates of all HA-VTE diagnosis between 1 in 141 and 532 admissions (14, 35), it is critical to target VTE prophylaxis strategies to only those patients at highest risk for developing VTE. Likewise, low-risk patients need to be identified to avoid exposure to the bleeding risks of anticoagulation and/or the cost and challenges of intermittent pneumatic compression device (IPC). The principal that the VTE development in hospitalized pediatric patients is multifactorial and that the strengths of the VTE risks vary lend this outcome to the use of RAMs. RAMs have been developed and validated for hospitalized adults, but few have been published for pediatrics (10, 36, 37). With the mandate imposed by 2014 Joint Commission on Accreditation of Healthcare Organizations for VTE risk assessment screening on all hospitalized adults (18 years and older), awareness of HA-VTE in children has been heightened, and the need for improved screening tools has been recognized (1).

Four RAMs based on risk factor identification for the development of VTE in hospitalized children have been published (Pediatric inpatients, **Table 1**) (18–20, 35). In these models, three to six independent risks factors were identified in case–control studies and a weighted score was assigned to the risk to derive a score. Common factors to all the models were increased length of stay and infection. In addition, the presence of CVCs and intubation/immobility were identified in more than one RAM. Several of these factors in children are also incorporated in validated adult RAMs, such as infection and immobilization (10, 36). However, older age, history of thrombophilia, and malignancy which were identified in adult RAM models were not found in these studies in children (10, 36, 37). The pediatric studies are challenged by small sample sizes, retrospective study design and lower incidence of VTE, which limit the power to detect potentially significant risk factors. Additionally, many of these models included length of stay which cannot be used in a prospective manner for VTE risk prediction. It should be noted that two RAMs in children with trauma and one in pediatric patients with acute lymphoblastic leukemia who have a high risk of VTE have also been developed and validated (**Table 1**); these RAMs were developed similarly by identification of VTE risks and weighting of factors based on odds ratios. These models have been validated in independent cohorts, but will need to be studied prospectively to determine their utility (28, 34, 38).

Risk-assessment models can be used to stratify VTE risk in order to better balance the risks and benefit of the prophylactic options. It has been suggested in adults that a population with a VTE frequency of 2% or higher should be targeted for pharmacologic prophylaxis, and populations with risks between 1 and 2% would be appropriate for mechanical prophylaxis (37). While VTE occurrence is reduced by a half with heparin prophylaxis in adults, these data are lacking in pediatrics. The benefits of prophylaxis must be weighed against the risks. In children, the bleeding risk for prophylactic low molecular weight heparin (LMWH) has been reported to be 0.8% for major bleeding and 3% for minor bleeding (39). The uncertainties of the risk/benefits of interventions in children add to the challenges of implementation of RAMs and require additional studies.

PREVENTION: MECHANICAL AND PHARMACOLOGICAL

Venous thromboembolism prevention strategies for hospitalized pediatric patients include early mobilization, mechanical, and/or pharmacologic prophylaxis. In an effort to minimize harm, the strategies generally have utilized early mobilization and mechanical prophylaxis in patients determined to be at moderate risk for VTE and pharmacologic interventions are reserved for those patients with the highest VTE risk (40, 41).

Early Mobilization

Encouraging maximal mobility of all hospitalized patients is a relatively simple approach for VTE prevention. Movement of

TABLE 1 | Pediatric risk-assessment models (RAMs) for hospital acquired venous thromboembolism.

RAM	Patient population	Number of factors	VTE risk factors (maximum points)	Comments
Pediatric Inpatients				
Colorado Children's Hospital (18)	Medical/ICU (age 0–21 years)	3	Intubation, infection, LOS ≥ 5days	3.6% probability of VTE with 3 factors
Peds-Clot Riley Hospital for Children and Children's Memorial Hospital (35)	Medical/ICU (age 0–20 years)	6	Immobilization (3), direct ICU admission (0.5), CVC (1), blood stream infection (1), OCP (2), LOS ≥ 7 days (2)	9.5 point risk score; Score of 3: sensitivity: 57–70%; specificity: 80–88% AUC: 0.852–0.89
Johns Hopkins All Children's Hospital (20)	Medical/Non-ICU (age 0–21 years)	3	CVC (5), infection (2), LOS ≥ 4 days (1)	8 point risk score; 8 points: 12.5% VTE; 7 points 1.1% VTE; ≤6 points 0.1% VTE
Johns Hopkins All Children's Hospital (19)	ICU, non-cardiac (age 0–21 years)	3	CVC (8), infection (1), LOS ≥ 4 days (6)	15 point risk score; 15 points: 8.8% VTE; 7–14 points 1.3% VTE; ≤7 points 0.03% VTE
Pediatric Trauma				
ROCKiT (Johns Hopkins Hospital trauma registry and National Trauma Data Bank) (28)	Trauma (age 0–21 years)	6	Older age (4), intubation (4), high ISS (7), low GCS (1), surgery (5), blood transfusion (2)	23 point risk score; score of 13: sensitivity: 87%; specificity: 81%; AUC: 0.9
National Trauma Data Bank (38)	Trauma (age 0–17 years)	10	Older age (147), female sex (4), ICU admission (171), intubation (97), low GCS (34), CVC (61), pelvic fracture (33), lower extremity fracture (36), major surgery (150), blood transfusion (58)	797 point risk score; >688 points: >5% VTE; 524–688 points 1–5% VTE; ≤523 points <1% VTE; AUC: 0.945
Pediatric Malignancy				
BFM/COALL/FRALLE acute leukemia protocol (34)	Acute lymphoblastic leukemia in induction therapy (age 1–18 years)	3	steroid/asparaginase (1), CVC (1), thrombophilia (2)	Maximum score range (3–4) depended on treatment protocol >2.5 points: 64.7% VTE ≤2.5 points 2.5% VTE

VTE, venous thromboembolism; ICU, intensive care unit; LOS, length of stay; CVC, central venous catheter; OCP, oral contraceptive pill; AUC, area under the curve; ISS, injury severity score; GCS, Glasgow Coma Scale; BFM, Berlin-Frankfurt-Münster 90/95/2000; COALL, Cooperative Acute Lymphoblastic Leukemia 92/95; FRALLE, French Acute Lymphoblastic Leukemia 2000.

the calf muscle with ambulation prevents venous stasis in the lower extremities which as previously discussed is one of the key risk factors for VTE development. Maximal activity should be encouraged no matter the patient's VTE risk. In addition, this strategy may also have other benefits. In adult studies, implementation of early and maximal mobility has been associated not only with decreased VTE occurrence but also decreased length of stay and improved cognitive and functional outcomes (42, 43).

Mechanical Prophylaxis

Mechanical prophylaxis includes the use of either IPCs or graduated compression stockings. Compression stockings provide circumferential pressure that gradually decreases from the ankle to the thigh. IPCs utilize intermittent inflation and deflation of a "sleeve" to increase venous return from the lower extremities mimicking that action of the calf muscles. In addition, IPCs have been demonstrated to activate systemic fibrinolysis which could theoretically promote clot dissolution (44–50).

Currently, there are no pediatric trials assessing the effectiveness of mechanical prophylaxis. Adult studies support the efficacy of mechanical interventions in preventing DVT and PE in a number of different clinical situations including post trauma, post-surgical, and the medically ill hospitalized patient (51–55). Until recently, questions remained regarding the efficacy of IPCs versus compression stockings. A recent prospective study of adult ICU patients compared the incidence of VTE in those patients receiving either IPC or compression stockings. Only IPC, and not compression stockings, was associated with a lower VTE incidence as compared with controls [0.45 (95% CI 0.22–0.95)] (51). In addition, a large meta-analysis in hospitalized medical patients also supported the finding that IPC is superior to compression stockings in preventing DVT (54).

Pharmacologic Prophylaxis

There are limited studies addressing efficacy and safety of anticoagulation (pharmacologic prophylaxis) for VTE prevention in pediatric patients. The 2012 Chest guidelines provide recommendations for therapeutic ranges for prophylactic anticoagulation (warfarin INR 1.3–1.9 or LMWH anti-Xa 0.1–0.3 U/mL) (56). They do not comment on indications for VTE prophylaxis in hospitalized pediatric patients (56). Much of what is currently used in pediatric patients is extrapolated from the adult literature, especially as it pertains to the adolescent patient with VTE risk factors that are similar to that of adults. There are numerous studies that have demonstrated efficacy of anticoagulation for reducing hospital acquired VTE in both surgical and non-surgical adult patients and its use is considered standard of care (11, 53). In pediatric patients at risk for VTE, anticoagulation with either a LMWH or subcutaneous unfractionated heparin (UFH) has been utilized for prophylaxis (40). While weight based dosing is used for LMWH, there are no weight based dosing guidelines for subcutaneous UFH which limits pediatric use. Low-dose UFH continuous infusions have also

been utilized, primarily in the post-surgery setting, but published data on efficacy is lacking (26). Currently, direct oral anticoagulants are not FDA approved for pediatric use and clinical trials are underway to assess safety and efficacy for both VTE treatment and prophylaxis. The use of direct oral anticoagulants could potentially revolutionize the prevention and treatment of pediatric thrombosis with the possibility of a convenient route of administration and no requirement for monitoring.

Central Venous Catheters

Unlike in adults, the most important risk factor for VTE in pediatric patients is the presence of a CVC. The 2012 CHEST guidelines recommend against primary prophylaxis after the placement of a central venous line (56). There are three randomized clinical trials that studied primary CVC prophylaxis in pediatric patients using prophylactic dosing of either LMWH (anti-Xa goal 0.1–0.3 U/mL), UFH (10 U/kg/h), or warfarin (INR goal 1.3–1.9) (26, 57, 58). None of these trials were able to demonstrate a difference in thrombotic events between the two treatment arms, although these studies were generally underpowered. Specifically, the number of subjects was too small to provide enough statistical power, and this was most commonly secondary to challenges with enrollment (56). A recent systematic review and meta-analysis of thromboprophylaxis in children was unable to find evidence that it reduced the risk of CVC-associated thrombosis (59). Ongoing research is needed to determine the most effective way to prevent CVC-associated thrombosis.

When considering prophylactic measures for VTE in hospitalized pediatric patients it is important to assess for potential harms from the intervention (60). Contraindications to mechanical prophylaxis include a device that does not fit the patient, distal peripheral IV access, skin, or lower extremity conditions that result in pain with compression (i.e., fracture, vaso-occlusive pain in a patient with sickle cell disease, burns, etc.) (60). Contraindications to anticoagulation include the presence of active bleeding, a concurrent coagulopathy (acquired or congenital), acute stroke, epidural catheter, uncontrolled severe hypertension, recent surgical procedure with a high risk of surgical site hemorrhage, or an intracranial mass (56).

VTE DETECTION AND DIAGNOSIS

Despite prevention efforts, thrombotic events can still occur in hospitalized pediatric patients, and it is imperative that VTE remain a consideration when concerning clinical signs and symptoms are present. The signs and symptoms of VTE are dependent on the site and degree of venous occlusion. When an extremity is affected the clinical signs include swelling and pain of that extremity. If there is embolization of the thrombus the patient may develop a sudden onset of pleuritic chest pain, shortness of breath, and/or persistent tachycardia. A large PE can present as acute respiratory and cardiac failure. In a patient who is intubated and unable to report symptoms a PE could present as an acute respiratory decompensation. For those patients with an abnormal connection between the right and left side of the heart, a venous embolism could become a paradoxical embolism with resultant stroke or distal ischemia to the gut, kidneys or limbs.

When VTE is suspected, the imaging modality selected is dependent on the site of thrombosis. Historically, venography was the gold standard, but it has increasingly fallen out of favor, being replaced by other imaging modalities like ultrasonography, CT, or MR venography (61). The D-dimer has not been validated in pediatric clinical trials for the diagnosis of VTE, and has only been studied as a risk for recurrence, making interpretation difficult in this population (62).

Early recognition and diagnosis of a hospital acquired VTE will ensure prompt treatment with full anticoagulation which will minimize VTE associated harms. The goal of anticoagulation is to stop clot propagation, prevent embolism (pulmonary and paradoxical), preserve vascular access and prevent bacteremia (56). In the clinical setting of a lower extremity DVT and an absolute contraindication to anticoagulation, a temporary inferior vena cava filter should be considered for children who weigh greater than 10 kg (56). The filter should be removed as soon as the contraindication has resolved and anticoagulation can be instituted.

SUMMARY

While HA-VTE is uncommon in children compared to adults, it is increasing and associated with significant morbidity. Validated risk-assessment tools to identify adult patients at high risk for the development of VTE in the hospital are in widespread use. Some risk factors for VTE are shared between children and adults; however, there are significant limitations for the use of these tools in children. Importantly, several pediatric RAMs have been published, but the studies are relatively small and need prospective validation. Strategies to identify pediatric patients at highest risk for HA-VTE are needed to target interventions to prevent non-CVC-associated VTE. Further studies assessing clinical outcomes of VTE prevention strategies are critical to assess the effectiveness and harm of prophylactic interventions in children. A major challenge remains with CVC-associated VTE, since currently there is no evidence that pharmacologic prophylaxis, or other interventions, are effective for prevention.

AUTHOR CONTRIBUTIONS

CW and CT both equally contributed to the drafting of the original manuscript and reviewed and approved of the final submitted version.

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MINI REVIEW
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Treatment of Venous Thromboembolism in Pediatric Patients

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Given the increased incidence of venous thromboembolism (VTE) in pediatric patients, which has been associated with increased survival of medically complex patients and increased use of invasive supportive measures, it is important to understand treatment options and unique aspects of anticoagulant use in children. The objective of this mini-review is to outline the goals of treatment, treatment options, and adverse events associated with the use of anticoagulants in pediatric patients with VTE.

Keywords: venous thrombosis, thromboembolism, pediatrics, treatment, anticoagulants

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BACKGROUND

Venous thromboembolism (VTE), especially hospital-acquired VTE, is increasingly recognized in pediatric patients. The incidence of VTE in hospitalized children has increased approximately 70% over a 6-year period and is thought to affect approximately 1 in every 200 hospitalized children (1). The rise in VTE is largely attributed to increased use of invasive support of critically ill patients, especially with the use of central venous access devices, which can lead to line-related VTE, and the improved survival of patients with complex medical conditions. Recent efforts have been made to better understand aspects of VTE in this patient population including risk factors for development of thrombosis, therapeutic outcomes, risks for recurrence, and long-term prognosis as these may differ from those in adult patients.

When considering treatment options in children, it is important to consider ways in which use of anticoagulants in pediatric patients may differ from adults. As outlined in the American College of Chest Physicians CHEST Guidelines for "Antithrombotic Therapy in Neonates and Children," some of these important differences include (1) "epidemiology of thromboembolism in pediatric patients differs from that seen in adults," (2) "hemostatic system is a dynamic, evolving entity that likely affects not only the frequency and natural history of thromboembolism in children but also the response to therapeutic agents," (3) "distribution, binding, and clearance of antithrombotic drugs are age dependent," (4) "limited vascular access reduces the ability to effectively deliver some antithrombotic therapies and can influence the choice of antithrombotic agent," (5) "specific pediatric formulations of antithrombotic drugs are not available, making accurate, reproducible dosing difficult," and (6) "dietary differences make the use of oral vitamin k antagonists particularly difficult" (2). With these considerations in mind, this article focuses on therapeutic options for VTE in children, which are important in order to optimize care and outcomes in this cohort.

GOALS OF TREATMENT

The goals of treatment of pediatric VTE overlap with those of adult patients. The initial goal of anticoagulation is to halt clot progression. With the initiation of parenteral or enteral anticoagulation, clot stabilization will typically occur, thus preventing a thrombus from expanding in length to involve additional venous segments, or expanding in circumferential diameter. Use of conventional anticoagulants will not cause clot breakdown, rather the body relies on its endogenous fibrinolytic system to dissolve the thrombus. Another important goal of treatment of VTE is the prevention of embolization of the thrombus from its original site to areas such as the lungs or central nervous system. When embolization does occur, it can substantially increase the morbidity and mortality associated with VTE (3).

With use of anticoagulation, an additional goal is prevention of VTE recurrence. The specific role of anticoagulation, including duration of therapy, is not clearly defined in regards to recurrence prevention. To date, no adequately powered pediatric study has addressed this issue; however, a current randomized controlled trial (RTC) is underway that has demonstrated feasibility in the initial pilot phase (4). The Duration of Therapy for Thrombosis in Children and Young Adults (Kids-DOTT) trial is a multicenter RTC investigating non-inferiority of a 6-week (shortened) versus 3-month (conventional) duration of anticoagulation in patients aged <21 years with provoked venous thrombosis with primary efficacy and safety endpoints of symptomatic recurrent VTE and anticoagulant-related bleeding.

In medically complex patients dependent on venous access for life sustaining measures, including those with congenital heart disease requiring repeated cardiac catheterization and short bowel syndrome requiring long-term parenteral nutrition, recurrent VTE that limits adequate venous access can become a life-limiting condition. In this setting, use of anticoagulants for secondary prophylaxis is often considered to reduce the risk of VTE recurrence. Data regarding efficacy of specific agents and complications in secondary prophylaxis in an RTC are largely lacking in pediatrics.

A potential debilitating long-term complication of VTE is the development of post-thrombotic syndrome (PTS). PTS arises as a result of chronic venous occlusion or valvular disruption leading to venous hypertension. Symptoms of PTS include limb heaviness, swelling, pain, cramping, and ulceration. Instituting anticoagulation early is crucial in order to minimize risk of clot propagation and to encourage clot resolution, both thought to reduce the risks of PTS in the pediatric patient population.

TREAMENT OPTIONS

The most common treatment options for VTE include unfractionated heparin (UFH), low molecular weight heparin (LMWH), and warfarin; other options include fondaparinux and the direct thrombin inhibitors (DTIs). This article will focus on the use of these parenteral and enteral anticoagulants; published data on the direct oral anticoagulants (DOACs) are not available at this time and thus will not be discussed in detail. Information regarding other modalities for management of VTE including thrombolytic agents and mechanical thrombolysis will be discussed elsewhere.

Heparins, including UFH and LMWHs, are a mainstay of initial VTE management in pediatric patients. UFH is often the first-line therapy in hospitalized pediatric patients who develop VTE and is used for primary prophylaxis of VTE in specific clinical settings including in individuals with congenital heart disease undergoing certain procedures or surgical interventions. UFH binds to antithrombin (AT), an endogenous anticoagulant, to induce a conformational change that makes AT a rapid inactivator of coagulation factors especially thrombin (Factor IIa) and Factor Xa. Binding of AT by heparin enhances the activity of AT on the order of 1,000- to 4,000-fold. In children, factors such as reduced levels of AT and prothrombin, reduced capacity to generate thrombin, and alterations in plasma binding may affect the action of UFH as compared to older individuals (5, 6).

Low molecular weight heparins are fragments of heparin with specific activity against activated factor X and less activity versus thrombin. Although the efficacy of LMWHs has not been proven in rigorous trials, they are used widely in pediatrics. Advantages of LMWH over UFH include a greater and more predictable bioavailability due in part to dose-independent clearance, longer duration of anticoagulation effect allowing for less frequent administration, and less frequent need for monitoring, which is importance in pediatric patients who may have poor venous access, and reduced complication rates of heparin-induced thrombocytopenia (HIT) and osteoporosis. LMWHs include enoxaparin (Lovenox®) and dalteparin (Fragmin®), noting that most clinical data available are a pediatric cohort with enoxaparin. Disadvantages of these LMWHs include twice daily subcutaneous injections, which can be problematic for some pediatric patients.

Fondaparinux (Arixtra®) is another anticoagulant utilized in pediatric VTE and is a synthetic pentasaccharide that causes an AT-mediated selective inhibition of factor Xa; unlike the LMWHs, fondaparinux has nearly pure anti-factor Xa activity. The advantages of fondaparinux over UFH are similar to those of the LMWHs; however, fondaparinux has some advantages over LMWH including once-daily dosing and no risk for neither HIT nor osteoporosis.

Another class of anticoagulants utilized in pediatric VTE, albeit infrequently, includes the DTIs. DTIs are short-acting agents that are more targeted than heparin and include the hirudin-like molecule bivalirudin, and small-molecule inhibitor argatroban, which are administered by continuous intravenous infusion. These molecules electively bind to and inhibit thrombin in both circulating and clot-bound forms. As compared to UFH, the pharmacokinetics are more predictable and these agents are not dependent on AT levels, which are physiologically low in children <6 months of age. These medications are used primarily in the setting of HIT, a rare but potentially life threatening condition mediated by IgG autoantibodies directed against platelet factor 4 in complex with heparin that occurs after heparin exposure.

Oral agents utilized in pediatrics patients for VTE thus far are limited to the vitamin K antagonist (VKA) warfarin (Coumadin®) in the United States. Warfarin works to inhibit the synthesis of vitamin K-dependent coagulant proteins, which include factors II, VII, IX, and X. Warfarin use in pediatrics is problematic in

that it requires frequent monitoring, has numerous drug interactions, is affected by dietary intake of Vitamin K, and has a narrow therapeutic range. Additionally, warfarin is only available as a tablet and cannot be compounded into a liquid formulation making administration in young children difficult. VKAs in neonates are especially problematic due to the physiologically low levels of vitamin K-dependent clotting factors and the overall low vitamin K content of breast milk. VKA use in older children in contrast is often feasible with caregivers and physicians needing to balance the burden of frequent laboratory monitoring with dose adjustments with a VKA with the need for subcutaneous injections utilizing LMWHs.

Direct oral anticoagulants such as the factor Xa inhibitors [rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Savaysa®)] and DTI [dabigatran (Pradaxa®)], which have been approved in adult patients for both treatment and prevention of VTE, neither have FDA-approved indications nor dosing in children that has yet been established. Use of these agents for children are appealing given that they are thought to require no specific monitoring and overall have a risk profile in adult studies that is equal to, or less than, VKAs. That said, extrapolation of adult data to pediatric patients at this time is premature and will not be addressed in this article. Fortunately, there are several clinical trials in pediatric patients addressing dosing, adverse events, and ultimately comparative efficacy versus standard anticoagulation of DOCAs that will ultimately guide their use in pediatrics.[1,2,3]

To date, comparative efficacy of various anticoagulants in pediatric patients has largely not been studied. The REVIVE trial was the first multicenter, international RTC to attempt to study comparative efficacy of anticoagulants (7). The study was an open-labeled RCT of LMWH compared to heparin and coumadin for the treatment of VTE in children that aimed to study the rates of recurrent VTE and death due to VTE during a 3-month treatment period. Unfortunately, the study was closed due to poor patient enrollment. Ongoing studies of the DOACs compared to anticoagulation currently used in pediatric patients will provide much needed data to guide hematologists on the specific safety and efficacy of these agents.

DOSING AND MONITORING

Dosing and monitoring guidelines in pediatrics have been established, often through extrapolation from adult data (**Table 1**). For UFH, no pediatric outcome-specific studies have established a pediatric range for UFH; therefore, therapeutic ranges have been generalized from adult VTE studies. Commonly, goals for therapeutic anticoagulation target an anti-Xa for UFH of 0.35–0.7 U/mL, thought to reflect to an activated partial thromboplastin time (aPTT) that correlates with a protamine titration of 0.2–0.4 U/mL (for purposes of this article an anti-Xa level of 0.35–0.7 will be assumed to reflect a aPTT of 60–85 s while acknowledging that this assumption may not hold true in pediatrics samples and will vary based on anti-Xa kit). Typically, initial UFH dosing involves a loading dose of 50–100 U/kg given intravenously over 10 min; there are little data to support this practice in pediatrics, especially in the neonatal population. Following initial bolus dose, maintenance dosing of 28 U/kg/h for infants (<1 year of age) and 20 U/kg/h for children ≥1 year is utilized. Choice of monitoring of anti-Xa for UFH versus aPTT in children is not well established and differs by institution. After initiation of UFH, anti-Xa/aPTT is then monitored 4–6 h post bolus and every 4–6 h after a dose adjustment (**Table 1**) (2). In patients who have difficulty achieving a therapeutic aPTT, checking AT levels is recommended, given AT supplementation may be required if sufficiently low.

Similar to UFH, therapeutic ranges for LMWH are largely extrapolated from adult VTE trials and are based on measurement of anti-Xa levels. For therapeutic dosing of LMWH, an anti-Xa of 0.5–1.0 U/mL from a sample obtained 4–6 h after a dose is considered in goal range; the initial anti-Xa level should be checked after the second or third dose is initiated. For patients receiving prophylactic anticoagulation to prevent recurrent VTE, an anti-Xa of 0.1–0.5 U/mL is typically considered goal. Dosing of LMWH varies by age with infants requiring often 50% increased dosing as compared to older children. Dosing for specific anticoagulants is listed in **Table 1**. Enoxaparin is the most widely utilized of the LMWHs in pediatrics and is typically initiated 2 mg/kg/dose every 12 h in preterm neonates, in 1.7 mg/kg/dose every 12 h in term neonates, 1.5 mg/kg/dose every 12 h for age <2 months, and 1 mg/kg/dose every 12 h for age ≥2 months (8, 9). Although enoxaparin has less activity against thrombin, in patients who have difficulty achieving a therapeutic anti-Xa level, checking AT levels to ensure that there is no significant AT deficiency should be considered. Fondaparinux is monitored using anti-Xa levels in a similar fashion to LMWHs and is initiated at a dose of 0.1 mg/kg/dose once daily.

Direct thrombin inhibitor use in pediatrics is largely in the setting of suspected or confirmed HIT. Anticoagulation goals have not been well established in this population. Argatroban manufacturer's dosing guidelines include pediatric usage noting that in critically ill pediatric patients dosing is typically started lower than in adult patients. In general, therapy with argatroban is monitored utilizing aPTT with initial monitoring preformed within 1–3 h from medication initiation in patients without hepatic impairment and approximately 2–4 h after a dose change. Goal aPTT is typically 1.5–3 times baseline value and avoidance of aPTT > 100 s. With argatroban, dosing is typically a continuous infusion of 0.75 and 0.2 μg/kg/min in those with hepatic impairment without a bolus.[4] As with argatroban, there is no established dosing range for bivalirudin in infants and children. The UtilizatioN of Bivalirudin on Clots in Kids (UNBLOCK) study found initial bolus dosing of 0.125 mg/kg followed by an initial infusion of 0.125 mg/kg/h of bivalirudin demonstrated efficacy

[1] Bayer. *EINSTEIN Junior Phase III: Oral Rivaroxaban in Children with Venous Thrombosis (EINSTEIN Jr)*. Available from: www.clinicaltrials.gov.

[2] Pfizer. *Apixaban for the Acute Treatment of Venous Thromboembolism in Children*. Available from: www.clinicaltrials.gov.

[3] Boehringer Ingelheim. *Open Label Study Comparing Efficacy and Safety of Dabigatran Etexilate to Standard of Care in Paediatric Patients with Venous Thromboembolism (VTE)*. Available from: www.clinicaltrials.gov.

[4] Argatroban. *GlaxoSmithKline*. Houston, TX. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020883s014lbl.pdf.

TABLE 1 | Dosing and adjustment of anticoagulants.

Class of medication/drug	Initial dosing	Subsequent dosing	Goal	Dose adjustment
UFH	50–100 U/kg IV (loading dose)	28 U/kg/h (age <1 year) 25 U/kg/h (age ≥1 year)	anti-Xa level 0.35–0.7/aPTT 60–85 s	aPTT <50 s; bolus 50 U/kg, increase by 10% aPTT <50–59 s; increase by 10% aPTT <60–85 s; no change aPTT <86–95 s; decrease by 10% aPTT <96–120 s; hold dose × 30 min, decrease by 10% aPTT <120 s; hold dose × 60 min, decrease by 15%
LMWH				
Enoxaparin	*Treatment dosing* 2 mg/kg/dose SC q 12 h (preterm neonates) 1.7 mg/kg/dose SC q 12 (term neonates) 1.5 mg/kg/dose SC q 12 h (age <2 months) 1 mg/kg/dose SC q 12 (age ≥2 months)		anti-Xa level 0.5–1 (treatment)	anti-Xa <0.35; increase dose by 25% anti-Xa 0.35–0.49; increase dose by 10% anti-Xa 0.5–1; no change anti-Xa 1.1–1.5; decrease dose by 20% anti-Xa 1.6–2; hold for 3 h and decrease dose by 30% anti-Xa >2; hold until anti-Xa 0.5–1 then decrease dose by 40%
	Prophylactic dosing 0.75 mg/kg/dose SC q 12 h (age <2 months) 0.5 mg/kg/dose SC q 12 h (age <2 months)		anti-Xa level 0.1–0.5 (prophylaxis)	anti–Xa <0.1; increase dose by 25% anti-Xa 0.1–0.5; no change anti-Xa 0.51–1; decrease dose by 20% anti–Xa >1; decrease dose by 30%
Dalteparin	129 ± 43 U/kg/dose SC q 24 h			
Fondaparinux	*Treatment dosing* 0.1 mg/kg SC q 24 h		anti-Xa level 0.5–1 (treatment)	anti-Xa <0.3; increase dose by 0.03 mg/kg anti-Xa 0.3–0.49; increase dose by 0.01 mg/kg anti-Xa 0.5–1; no change anti-Xa 1.1–1.2; decrease dose by 0.01 mg/kg anti-Xa >1.2; decrease dose by 0.03 mg/kg
	Prophylactic dosing 0.05 mg/kg SC q 24 h		anti-Xa level 0.1–0.5 (prophylaxis)	anti-Xa <0.1; increase dose by 25% anti-Xa 0.1–0.5; no change anti-Xa 0.51–1; decrease dose by 20% anti-Xa >1; decrease dose by 30%
VKA				
Warfarin	0.1–0.2 mg/kg (max dose 5 mg) PO q 24 h		INR 2–3	*Day 2–4 consider dose adjustment in day 2–4* INR 1.1–1.3; repeat initial dosing INR 1.4–3.0; give 50% of loading dose INR 3.1–3.5; give by 25% of loading dose INR >3.5; hold until INR <3.5 then restart at 50% dosing *Maintenance* INR 1.1–1.4; increase by 20% INR 1.5–1.9; increase by 10% INR 2.0–3.0; no change INR 3.1–3.5; decrease by 10% INR >3.5; hold until INR <3.5; restart at 20% decreased dosing
DTI				
Argatroban	0.75 μg/kg/min IV 0.2 μg/kg/min IV (hepatic impairment)		aPTT 1.5–2.5× baseline	
Bivalirudin	0.125–0.25 mg/kg (loading dose) IV	0.125–0.2 mg/kg/h	aPTT 1.5–3× baseline	

UFH, unfractionated heparin; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; DTI, direct thrombin inhibitor; IV, intravenously; SC, subcutaneously; PO, orally; aPTT, activated partial thromboplastin time; INR, international normalized ratio; anti-Xa, anti-Factor Xa level.

and reassuring safety in a cohort of pediatric patients with acute VTE (10). Historically, monitoring of bivalirudin utilizing aPTT with a goal of 1.5–2.5× the baseline aPTT has been suggested; however, the UNBLOCK study demonstrated poor correlation between aPTT and plasma bivalirudin concentration suggesting limited utility of aPTT monitoring with this drug.

As with adult patients utilizing VKAs, target international normalized ratios (INRs) for anticoagulation are typically 2.0–3.0; to date, there have been no clinical trials to address optimal INRs for a pediatric cohort. In patients requiring anticoagulation for mechanical heart valves, a target INR of 2.5–3.5 mimic target INRs was fixed for adult patients. Warfarin is begun at a dose of 0.1 mg/kg, or alternatively with a loading dose of 0.2 mg/kg (maximum dose of 5 mg), with daily monitoring and dose adjustment in the first 5 days (**Table 1**) followed by monitoring of maintenance dosing (2). During the first 5 days of VKA use, and until the INR is at least 2.0 for two consecutive days, a heparin product should be utilized. This "bridging anticoagulant" is used to prevent against warfarin-induced skin necrosis, which occurs due to a relative decrease of vitamin K-dependent endogenous anticoagulants prior to a decrease of endogenous procoagulants. Repeat INR testing needs to be considered with changes to concomitant medication use or medical illness.

DURATION OF THERAPY

Duration of therapy for VTE in pediatric patients has been less well defined and is largely extrapolated from adult data. A recommendation of a 3-month course of anticoagulation for pediatric patients with provoked VTE has been based on the results of clinical trials in adults with a shorter, 6-week course, of anticoagulation considered in certain pediatric patient populations; these recommendations have not been based on evidence from pediatric trials. The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines provides guidance for duration of therapy for pediatric patients with VTE in various settings, including consideration of longer duration of therapy in the setting of serious, unprovoked thrombosis and is largely used in pediatric practice to guide duration therapy (2). Notably, the pediatric recommendations from the CHEST Guidelines are largely based on expert opinion, case series, and relatively small studies rather than large RTCs, which have guided treatment recommendations in adult population.

ADVERSE EVENTS

With the use of any anticoagulant, the primary adverse event of therapy is bleeding. Given the lack of comparative efficacy studies in pediatrics, no adequately powered study has compared bleeding rates of one drug compared to another for treatment of UFH-related bleeding, given the short half-life of the medication, discontinuation of the medication is often sufficient. In the event of more severe bleeding or when immediate reversal may be needed preoperatively, use of protamine sulfate will rapidly neutralize UFH; guidelines for reversal are available (**Table 2**) (2). Although limited data are available for LMWH-related bleeding in the setting of overdosage, use of protamine can be considered (**Table 2**).[5,6] It is important to note that the anti-Xa activity is never completely neutralized; with enoxaparin a maximum of 60% and dalteparin a maximum of 60–75%, of the anti-Xa activity is neutralized.

Adverse events such as HIT are relatively rare in the pediatric population; however, this poses a potentially life threatening complication and narrows options for VTE treatment. Rates of HIT in pediatrics range from 0 to 3.7% (11). In adult patients, the pretest clinical scoring system commonly used known as the 4T score is not applicable in pediatric patients given the overall rarity of HIT in children versus adults.

For those individuals who require long-term preventative anticoagulation, other considerations need to be made such as the risk of osteoporosis with heparins. In adult patients, exposure

[5]Lovenox. *Sanofi-Aventis*. Bridgewater, NJ. Available from: http://products.sanofi.us/lovenox/lovenox.html#section-12.

[6]Dalteparin. *Pfizer*. New York, NY. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020287s062lbl.pdf.

TABLE 2 | Anticoagulant reversal options for bleeding patients and over dosages.

Class of medication/drug	Reversal strategy	Time since last dose of anticoagulant medication	Dosage of reversal agent
Unfractionated heparin	Protamine	<30 min 30–60 min 60–120 min >120 min	1 mg protamine per 100 U of heparin 0.5–0.75 mg protamine per 100 U of heparin 0.375–0.5 mg protamine per 100 U of heparin 0.25–0.375 mg protamine per 100 U of heparin
Low molecular weight heparin			
Enoxaparin	Protamine	≤8 h >8 h	1 mg protamine per 1 mg enoxaparin 0.5 mg protamine per 1 mg enoxaparin
Dalteparin	Protamine	N/A If bleeding 2–4 h after first protamine dose	1 mg protamine per 100 U of dalteparin 0.5 mg protamine per 100 U of dalteparin
Vitamin K antagonist (VKA)			
Warfarin	Vitamin K	N/A; if international normalized ratios >10 and no bleeding	
	Four-factor prothrombin complex concentrate	N/A; if VKA-associated major bleeding occurs	

to LMWH beyond 3–6 months may adversely affect bone mineral density; large epidemiologic studies of osteoporosis in pediatric patients with long-term heparin/LMWH exposure have not been conducted, but given the relationship between heparin use and osteoporosis in adults, this should likely be avoided in pediatric patients as well (12, 13).

CONCLUSION

Given the increasing incidence of VTE in pediatric patients, it is crucial to understand treatment options for VTE including ways in which the hemostatic system and anticoagulant dosing and monitoring are different in this cohort as compared to adult patients. Notably, there is a lack of robust research aimed at addressing dosing, monitoring, safety, comparative efficacy, and duration of therapy to guide optimal care in pediatric patients, which offers areas for research focus for the future.

AUTHOR CONTRIBUTIONS

LM and GY conceptualized and researched the article and participated in manuscript preparation.

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MINI REVIEW
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Pediatric Thrombolysis: A Practical Approach

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The incidence of pediatric venous thromboembolic disease is increasing in hospitalized children. While the mainstay of treatment of pediatric thrombosis is anticoagulation, reports on the use of systemic thrombolysis, endovascular thrombolysis, and mechanical thrombectomy have steadily been increasing in this population. Thrombolysis is indicated in the setting of life- or limb-threatening thrombosis. Thrombolysis can rapidly improve venous patency thereby quickly ameliorating acute signs and symptoms of thrombosis and may improve long-term outcomes such as postthrombotic syndrome. Systemic and endovascular thrombolysis can result in an increase in minor bleeding in pediatric patients, compared with anticoagulation alone, and major bleeding events are a continued concern. Also, endovascular treatment is invasive and requires technical expertise by interventional radiology or vascular surgery, and such expertise may be lacking at many pediatric centers. The goal of this mini-review is to summarize the current state of knowledge of thrombolysis/thrombectomy techniques, benefits, and challenges in pediatric thrombosis.

Keywords: pediatric thrombosis, pediatric thrombolysis, DVT therapy, pediatric DVT, thrombolysis, combination therapy

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INTRODUCTION

The incidence of pediatric venous thromboembolism (VTE) is estimated to be 0.07–0.14/10,000 children (1, 2), and data suggest that the incidence of thrombosis in children is dramatically increasing (3). This increase may be due in part to the advancement in the management and invasive supportive care of critically ill children and improved imaging modalities to diagnose VTE. Several risk factors for pediatric thrombosis have been identified, including the presence of a central venous catheter (CVC), cancer, congenital heart disease, and surgery (4).

The mainstay of therapy of acute pediatric thrombosis is anticoagulation, and the goals of anticoagulation are to prevent propagation of acute thrombosis, prevent recurrence, and prevent embolization. The most commonly used anticoagulants are unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and vitamin K antagonists (5). Unfortunately, anticoagulation alone does not rapidly restore the patency of occluded vessels, and in patients at high risk for acute venous insufficiency, VTE recurrence, or postthrombotic syndrome (PTS), anticoagulation may not be enough to achieve optimal outcomes. Moreover, the additional risk factors for and the frequency of adverse outcomes in pediatric thrombosis remain poorly understood. Recurrent thrombosis can occur in 7–8% of children (2, 4). It is estimated that nearly 2% of pediatric venous thrombosis

will directly result in death (4), with 4–9% mortality in arterial thrombosis (6). Long-term complications can include limb-length discrepancies and claudication with arterial thrombosis (7), and PTS with venous thrombosis. PTS is the most common chronic complication of VTE and can manifest as pain, edema, and venous stasis ulcers; PTS can limit age-appropriate activities, resulting in a significant impact on children's quality of life (8). PTS is seen in about 26% of children with extremity venous thrombosis (9).

Thrombolysis has been used in pediatrics for decades (10–15), but in the last 10–20 years, its use has gained momentum with the improved capability of laboratory monitoring, radiologic imaging, interventional radiology, and surgical interventions. In pediatrics, one can consider two broad groups of patients that account for most thrombolysis therapy for VTE. The first group of candidates for thrombolysis may be children and adolescents who present with community(home)-acquired VTE. The second group consists of children with complex congenital heart disease or chronic conditions who develop venous insufficiency related to abnormal hemodynamics, surgical interventions, and life-dependence on CVCs (16, 17). Yet, without high-quality clinical trials of thrombolysis in pediatric thrombosis, providers are left without clear indications for the use of thrombolysis and without uniform dosing regimens. Most importantly, we have limited data on the risks and outcomes of thrombolysis. With this in mind, we will review current data on thrombolysis and offer guidance on its use in pediatric thrombosis outside of the central nervous system.

BACKGROUND

Fibrinolytic System

The fibrinolytic system is a dynamic system that continues to develop following birth (14), and is regulated by various cofactors and inhibitors (18). During fibrinolysis, the zymogen plasminogen is activated by two main serine proteases, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). tPA binds to fibrin at lysine binding sites and converts plasminogen into plasmin. uPA has no fibrin specificity and can activate both fibrin-bound and circulating plasminogen (14). Both activators have a short half-life of 4–8 min due to the actions of circulating inhibitors: plasminogen activator inhibitor (PAI-1), thrombin-activatable fibrinolysis inhibitor (TAFI), and alpha-2 antiplasmin, which inactivate plasmin or impair plasmin formation (18).

Neonates and infants have qualitative and quantitative differences in plasminogen compared with older children and adults (19). Plasminogen levels increases to adult levels by 6 months of age (20). TPA is also decreased at birth while PAI-1 levels are normal or increased; levels of tPA and PAI-1 do not reach adult levels until late adolescence. Thus, fibrinolysis throughout childhood may be downregulated. Low levels of plasminogen have been shown to impact the actions of pharmacologic thrombolytics (21), but there are insufficient data to demonstrate what effect, if any, high levels of PAI-1 or other fibrinolysis inhibitors may have on the activity of thrombolytic therapy throughout childhood.

PHARMACOLOGIC AGENTS

In contrast to anticoagulants that decrease the body's ability to form new thrombus, thrombolytic agents act by converting plasminogen to plasmin and thereby actively reduce clot burden. Several thrombolytics have been used in pediatrics: streptokinase, urokinase, and recombinant tPA (rtPA). In an *in vitro* model of thrombolysis using the three agents, streptokinase showed the slowest rate for clot lysis, tPA had improved lysis early on, and urokinase showed better fibrinolytic specificity (22). Recombinant tPA has a high affinity for fibrin, and the fibrin-tPA complex enhances the binding of plasminogen to fibrin, localizing the effects to the site of thrombosis. rtPA is recommended in pediatrics over other thrombolytics (23), and our review will focus on rtPA.

Recombinant tPA was first FDA approved in the 1980s (24) and initially was used in adults for coronary artery thrombolysis and has since been widely used for stroke (25) and unstable pulmonary embolism (26). The earliest reports in pediatrics were the use of systemic rtPA for catheter-associated arterial thrombosis (11, 13) and pulmonary embolism (12). There are several formulations of rtPA: alteplase with a half-life of 3–5 min, and two modified rtPAs: reteplase® with a half-life of 13–16 min, and tenecteplase with a half-life of 20–24 min. Alteplase is most commonly used in pediatrics due to its short half-life, and dosing for thrombolysis in children is not standardized.

GENERAL CONSIDERATIONS

Recommended Resources

To improve the safety of and optimize outcomes in patients receiving thrombolysis, a multidisciplinary approach is needed (27). The ability to quickly obtain coagulation testing results for ongoing adjustments in therapy is critical for managing patients receiving thrombolysis and concomitant anticoagulation. Thrombolysis should occur in the critical care setting to allow for rapid intervention should bleeding occur. Access to imaging modalities such as duplex ultrasound, computed tomography, and magnetic resonance imaging also allows for the necessary surveillance of thrombolysis. For endovascular thrombolysis, experienced interventional radiologists or interventional cardiologists familiar with techniques in young patients must be available.

Laboratory Monitoring

Whether systemic or endovascular thrombolysis is used, concomitant use of anticoagulation is recommended to prevent new thrombus formation during thrombolysis, as clot lysis releases active thrombin which was bound to thrombi (28). Reported dosing of concomitant anticoagulation has ranged from therapeutic UFH to UFH at a set dose of 5–10 units/kg/h (29–31). While UFH therapy alone can be monitored using either aPTT or anti-Xa levels, anti-Xa levels should be monitored during thrombolysis when possible. Fibrin split products can prolong the activated thromboplastin time (aPTT), thus aiming for a specific aPTT is of unclear utility during thrombolysis. Infants or any child with suspected acquired plasminogen deficiency should receive fresh frozen plasma prior to initiation of thrombolysis.

Careful laboratory monitoring during thrombolysis is required, with hemoglobin/hematocrit, platelet count, fibrinogen, fibrin degradation products, D-dimer, aPTT, prothrombin time, and UFH anti-Xa levels done every 6–12 h. D-Dimer levels can help direct systemic thrombolysis therapy, as a normal or low D-dimer indicates a lack of thrombolysis and can be used to guide dose increases, while an elevated D-dimer indicates that chemical activation of fibrinolysis has been achieved. A current blood type and screen is also recommended for any patient receiving thrombolysis, as is a renal panel for patients requiring contrast for venography or undergoing mechanical thrombolysis, due to a risk of hemolysis with the latter.

Timing of Thrombolysis

In general, thrombolysis is used in acute thrombosis of less than 14 days duration of vessel occlusion. In one study assessing efficacy of systemic thrombolysis, 83% of patients with thrombus less than 2 weeks had full or partial response to rtPA compared with 25% in those patients where the thrombus was older (32). For endovascular pharmacomechanical thrombolysis, though, some investigators suggest that more than 60 days from the onset of symptoms is a contraindication (33), although recent attempts to revascularize chronic venous occlusions are proving promising and can be considered for high-risk thrombi (34, 35).

Precautions and Contraindications

Several precautions should be taken during thrombolysis:

A. No arterial punctures or line placements.
B. No intramuscular injections.
C. Minimal manipulation of the patient (e.g., no chest physiotherapy).
D. No urinary catheterization, rectal temperatures, nasogastric tube placement.
E. Blood samples should be obtained from a superficial vein or indwelling catheter.
F. Avoid concurrent NSAIDs or anti-platelet therapy.
G. Intracranial imaging should be considered prior to and after thrombolytic therapy in children less than 3 months of age or any child at high risk for ischemic or hemorrhagic stroke.

While the decision to use thrombolysis should be made on a case-by-case basis, weighing pertinent risks, and benefits, there are general contraindications to thrombolysis that should be considered (27, 36).

A. Active bleeding.
B. Concurrent bleeding diathesis: inability to maintain platelets greater than 100,000/μl and fibrinogen above 100 mg/dL using transfusion support.
C. Recent major surgery or trauma, puncture of a noncompressible vessel, or organ biopsy within the previous 10 days.
D. Intracranial hemorrhage, infarction or intracranial or spinal surgery within the last 2 months.
E. Known right-to-left intracardiac shunt.
F. Cardiopulmonary resuscitation or asphyxia within 7 days of therapy (including complicated birth).
G. Extreme prematurity.

Other contraindications to thrombolysis have included pregnancy or puerperium; presence of intracranial vascular malformations, aneurysms or neoplasms; uncontrolled hypertension; infective endocarditis; and any contraindication to the use of unfractionated heparin or radiographic contrast media (if needed for assessment of thrombosis) (27).

INDICATIONS AND PATIENT SELECTION

Acute or subacute occlusive venous or arterial thrombosis that is limb- or life-threatening is the primary indication for thrombolysis. Thrombolysis can improve limb and organ perfusion by improving vessel patency and may quickly improve symptoms. Consensus guidelines offer indications for thrombolysis (23), but its use must be carefully considered due to the potential higher risk of major bleeding compared with anticoagulation alone.

Strong Indications for Thrombolysis

A. Arterial thrombosis with tissue ischemia.
B. Phlegmasia alba/cerulea dolens: extensive venous thrombosis with total occlusion of venous flow, increased compartment pressures and compromise of arterial blood flow (37).
C. Pulmonary embolism (PE) with hypotension or shock, or PE resulting in right heart strain or myocardial necrosis.
D. Superior vena cava syndrome.
E. Bilateral renal vein thrombosis.
F. Congenital heart disease with shunt thrombosis.
G. Large (>2 cm), mobile right atrial thrombus.
H. Kawasaki disease with coronary artery thrombosis.
I. Cerebral sinovenous thrombosis with neurologic impairment and no improvement with anticoagulation or progressive thrombosis.

Possible Indications for Thrombolysis

In the past decade, there have been reports of the use of thrombolysis in children for indications beyond acute limb- or life-threatening situations (31, 33, 38, 39). The goal of therapy in these cases is often to improve long-term outcomes or to maintain venous patency in children dependent on central venous access (17). Small prospective and retrospective case series suggest that the use of thrombolysis may be indicated for occlusive, symptomatic iliofemoral or inferior vena cava DVT to acutely decrease pain and improve function and, long-term, to potentially decrease the risk of (PTS) (31, 33, 38). Thrombolysis has been shown to decrease PTS in adults (40). Venous compression syndromes such as May-Thurner (41, 42) and Paget Schroetter (43) (effort thrombosis) have also been treated with combined thrombolysis and endovascular or surgical techniques. **Table 1** shows the results of published case series or cohort studies and demonstrates convergent results in thrombolysis efficacy, and rates of recurrence, PTS, and major bleeding.

METHODS OF THROMBOLYSIS

The choice of either systemic or endovascular thrombolysis depends on several factors. Foremost, is the availability of interventional radiologists/cardiologists who have pediatric expertise

with delivering site-directed endovascular treatment. There are sparse data on endovascular thrombolysis in certain anatomic areas such as the pulmonary vasculature (45), or cerebral venous sinuses (46), so systemic thrombolysis, rather than endovascular, is recommended for these sites. Another factor that may impact the mode of thrombolysis is the acuity of impending loss of life or limb, as the time to coordinate endovascular thrombolysis may be prohibitive. Also, a patient at higher risk of bleeding may benefit from endovascular thrombolysis as some data suggests that endovascular thrombolysis has a lower risk of bleeding than systemic thrombolysis (47).

Systemic Thrombolysis

Systemic thrombolysis is the intravenous administration of thrombolytics distant from the site of thrombosis. Case series using rtPA in children have used various dosing regimens with differing rates of success (29, 48, 49). A low-dose rtPA infusion and a high-dose (previously referred to as "standard dose") rtPA regimen have been described, with low-dose therapy showing equivalent efficacy to a high-dose regimens (29, 30). High-dose rtPA can be used for 6 h at a time and may be repeated over a 72-h period if imaging suggests no response. Low-dose rtPA can be a continuous infusion over 6–72 h, with close laboratory monitoring and imaging at a minimum of daily. **Table 2** describes dosing regimens.

In a review of pediatric thrombolysis, the reported overall number of patients with complete or partial resolution of thrombosis with systemic thrombolysis was 79%, with an incidence of major bleeding in 15% (47). Major bleeding is most often defined as fatal bleeding, bleeding resulting in a drop in hemoglobin of 2 g/dL or more within 24 h, retroperitoneal, pulmonary or intracranial, and bleeding requiring surgical intervention (50). Major bleeding events in children receiving systemic thrombolysis are often associated with longer tPA infusion times and a lower fibrinogen level immediately after thrombolysis (48).

Endovascular Thrombolysis

No studies have compared endovascular to systemic thrombolysis in children. Advantages of directed therapy are lower doses of rtPA, with potentially less risk of bleeding, and the ability to

TABLE 1 | Published results of thrombolysis in children.

Author	Method	*N*	Age, range and site of thrombosis	Lysis[a]	Major hemorrhage	SAEs, other	Recurrent VTE	PTS
Manco-Johnson (28)	Systemic UK/UH	32	6 weeks to 17 years and UE, LE, SVC, IVC, PE, atrial	50%	0	Death 1; PE 1; progress 1	9%	11.1% MJ
Wang (29)	Systemic TPA	12 HD 17 LD	1 day to 17 years and LE, UE, PE, CSVT, renal, hepatic, arterial, and venous	92% 100%	0 1 ICH, PT infant	1 embolic stroke with left atrial thrombus	0	8% 0% MJ
Goldenberg (38)	Systemic/PPMT	9	1–21 years and LE	89%	1 pulmonary	0	0%	11.1% MJ
Goldenberg (33)	CDT/PMT/PPMT	16	11–19 years and LE and UE	88%	0	PE 1	27%	13% MJ
Darbari (39)	CDT/PMT/PPMT	34	13 days to 21 years and LE and UE	17%(52%) 50 (99%)	1 2 required prbcs	0%	NA	NA
Dandoy (31)	CDT/PMT/PPMT	41	3 months to 21 years and LE, UE, SVC, and IVC	90% (>50%)	1 Required prbcs	PE 1	NA	14% (V or mV)
Gaballah (55)	CDT/PMT/PPMT	57	1–17 years and LE	33% (93.7%) >50%	1.8%		12%	2.1%V 59.3% mV

[a]*Lysis indicates 90–100% clot lysis; studies reports indicating 50–99% lysis or >50–% lysis are so noted.*

N, number of cases; SAE, serious adverse events; VTE, venous thromboemobolism; PTS, postthrombotic syndrome; UK, urokinase; UH, unfractionated heparin; TPA, tissue plasminogen activator; ICH, intracranial hemorrhage; PT, preterm; PE, pulmonary embolism; MJ, Manco-Johnson PTS scale; PPMT, percutaneous pharmacomechanical thrombolysis; CDT, catheter-directed thrombolysis; PMT, percutaneous mechanical thrombolysis; prcs, packed red cells; NA, not available; V, Villalta PTS scale; mV, modified Villalta PTS scale. LE, lower extremity; UE, upper extremity; SVC, superior vena cava; IVC inferior vena cava.

TABLE 2 | Dosing of alteplase and heparin during thrombolysis.

Mode of thrombolysis	Alteplase dosing		Duration of thrombolysis	Concomitant UFH therapy	Laboratory monitoring
	Bolus	Infusion			
Systemic thrombolysis	None None	Low-dose: 0.01–0.06 mg/kg/h (max 2 mg/h) High-dose: 0.1–0.5	6–72 h 2–6 h, may repeat if indicated	Prophylactic UFH with goal UFH anti-Xa level of 0.1–0.3 *or* UFH at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa
Site-directed thrombolysis	0.1–0.3 mg/kg (max dose 10 mg)	0.01–0.03 mg/kg/h *or* max 1–2 mg/h	Up to 72—96 h	Therapeutic UFH with goal UFH anti-Xa level of 0.3–0.7 *or* ufh at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa, renal profile, urinalysis

instill the thrombolytic agent directly into or near the thrombus. Endovascular thrombolysis is invasive, and is more costly than systemic thrombolysis due to the need for pediatric intensive care for up to 4 days, requirement of general anesthesia, use of interventional radiology expertise and suite for up to three sessions. In a systematic review of pediatric thrombosis, endovascular thrombolysis resulted in complete resolution in 76%, partial resolution in 17%, and no resolution in 7% of cases (47). Endovascular thrombolysis can be done over 12–96 h and can include several interventions (51):

A. Infusion-only, catheter-directed thrombolysis (CDT): This is the placement of a catheter under radiologic imaging directly into the thrombus to deliver thrombolytic agent.
B. Percutaneous mechanical thrombolysis/thrombectomy (PMT): This is the use of intravascular aspirating-type devices without thrombolytic to mechanically remove thrombus. This form of thrombolysis is discouraged because of the possibility of vascular injury and is used when thrombolytics are contraindicated.
C. Percutaneous pharmacomechanical thrombolysis (PPMT): This is the combined use of CDT with a device that mechanically breaks up the thrombus. A commonly used device in children is the Angiojet™, which uses high-velocity saline jets to generate strong negative pressures to break up and suction out the thrombus. The availability of Angiojet 4Fr devices allows for use in small vessels. The Ekos™ system uses ultrasound to instill tPA into the clot and is also gaining acceptance. These devices may cause significant hemolysis (52); intravenous hydration and monitoring of serial creatinine/renal function and electrolytes is recommended.

There is no standard protocol or preferred device in pediatrics, and use of any of these modalities is often physician-dependent. By allowing direct access to the occluded vessel, endovascular therapy can allow for additional techniques such as angioplasty and stent placement to improve vessel patency. Retrievable IVC filters may be placed at the time of endovascular thrombolysis to prevent embolization (53) but are not always necessary and are placed at the discretion of the interventionalist. If placed, IVC filters can be removed at the end of the procedure or within 3 months of placement. Pulmonary embolism is a known complication of endovascular thrombolysis and has been reported in 1–3% (44, 54). Major bleeding in children undergoing endovascular thrombolysis has been reported to be 0–3% (31, 33, 39, 55). Surgical thrombectomy has been reported in severe pediatric thrombosis where anticoagulation and thrombolysis have failed (56), cardiac ventricular thrombosis (57), and IVC thrombosis associated with abdominal tumors (58). Surgical thrombectomy should be reserved for the direst cases.

MANAGEMENT OF BLEEDING COMPLICATIONS

Bleeding is the most feared complication of thrombolytic therapy. Transfusion of cryoprecipitate should be given for hypofibrinogenemia (<100 mg/dL) and the platelet count should be maintained above 100 K/μL during thrombolysis. Menstruating females may receive non-estrogen-containing hormonal suppression with norethindrone before or during thrombolysis. Minor bleeding, such as bleeding from intravenous lines or catheterization site, can be managed with local control (pressure bandages or topical hemostatic agents, e.g., topical thrombin.) If more extensive bleeding occurs, the rtPA infusion can be decreased or temporarily stopped for at least 1 h. Anticoagulation can also be held or the dose lowered if bleeding persists. When bleeding is controlled, the anticoagulation can then be started at lower dose if previously stopped, and the rtPA infusion can be restarted at a lower dose. For major bleeding, such as intracranial or intra-abdominal bleeding, anticoagulation and rtPA should be stopped and cryoprecipitate should be administered. UFH can be reversed with protamine (1 mg of protamine for 100 U of heparin, maximum protamine dose is 50 mg/dose), and an antifibrinolytic such as aminocaproic acid or tranexamic acid be administered (23), although antifibrinolytics are not standard in this setting. Emergent surgical intervention may be required for major bleeding.

SUMMARY AND CONCLUSION

As the incidence of thrombosis in children increases, providers must be aware of treatment options to optimize outcomes. PTS occurs in nearly 30% of pediatric patients with thrombosis, which can cause life-long signs and symptoms of limb swelling, pain, and limitations in normal activities. Adult studies suggest that that thrombolysis decreases the risk of PTS by a third (59), and data in pediatrics also suggest that thrombolysis can significantly decrease the incidence of this complication (38). As children are expected to live for decades after a DVT, providers should strongly consider treatment modalities that may decrease the risk of this chronic complication. Thrombolysis can be safely performed in children but requires extensive monitoring and collaboration with hematology, critical care, and in cases of endovascular therapy, interventional radiology or interventional cardiology. Until randomized trials are performed to assess the benefits, risks, and complications of thrombolytic therapy in children, clinicians will need to continue careful patient selection and establish short- and long-term monitoring of patients treated with this therapy.

AUTHOR CONTRIBUTIONS

CT wrote the manuscript. MM-J reviewed the manuscript.

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Prevention of Hospital-Acquired Venous Thromboembolism in Children: A Review of Published Guidelines

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Venous thromboembolism, which includes deep venous thrombosis and pulmonary embolism, is a potentially preventable condition in children. In adults, pharmacologic prophylaxis has been shown to significantly reduce the incidence of venous thromboembolism in distinct patient cohorts. However, pediatric randomized controlled trials have failed to demonstrate the efficacy of pharmacologic prophylaxis against thrombosis associated with central venous catheters, the most important risk factor for venous thromboembolism in children. Despite the lack of supporting evidence, hospital-based initiatives are being undertaken to try to prevent venous thromboembolism in children. In this study, we sought to review the published guidelines on the prevention of venous thromboembolism in hospitalized children. We identified five guidelines, all of which were mainly targeted at adolescents and used various risk-stratification approaches. In low-risk children, ambulation was the recommended prevention strategy, while mechanical prophylaxis was recommended for children at moderate risk and pharmacologic and mechanical prophylaxis were recommended for the high-risk group. The effectiveness of these strategies has not been proven. In order to determine whether venous thromboembolism can be prevented in children, innovative clinical trial designs are needed. In the absence of these trials, guidelines can be a source of valuable information to inform our practice.

Keywords: child, deep venous thrombosis, guideline, heparin, pulmonary embolism, prophylaxis, randomized controlled trial

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BACKGROUND

In the past decade, the incidence of venous thromboembolism (VTE) in children has steadily increased. On average, the incidence increased by nearly 10% per year (1). VTE, which is composed mainly of deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with prolonged duration of mechanical ventilation and prolonged stay in the pediatric intensive care unit (PICU) and in the hospital (2). The excess hospital stay drives the increased cost associated with VTE in hospitalized children (3). In some cases, VTE may lead to death (4). The increasing incidence of VTE in children is thought to be the result of improved survival in critically ill children (1). It is also likely that a heightened awareness of VTE has contributed to increased diagnosis.

Hospital-acquired VTE is preventable in adults (5–7). Multiple randomized controlled trials (RCTs) in adults have demonstrated the superiority of pharmacologic prophylaxis, compared to

placebo, in reducing the incidence of VTE in targeted high-risk populations. It is possible that VTE is also preventable in children. In fact, the Solutions for Patient Safety network, a national collaborative of children's hospitals in the United States, has aimed to reduce harm from hospital-acquired VTE (8). However, in contrast to adults, data are lacking to support the use of pharmacologic prophylaxis in children. Pediatric RCTs of prophylaxis have focused on central venous catheter (CVC)-associated DVT (CADVT) because this is the most important cause of DVT in children. In a systematic review of RCTs of CADVT, Vidal et al. analyzed two RCTs on heparin-bonded CVC, three on infusions of unfractionated heparin at doses of ≤10 U/kg/h, one on reviparin [a low molecular weight heparin (LMWH)] at prophylactic dose, one on warfarin, one on antithrombin concentrate, and one on nitroglycerin (9). None of them were efficacious. Relative risks of CADVT with intervention ranged from 0.06 to 1.53, none of which were statistically significant. Despite the lack of supporting evidence, hospital-based initiatives are being undertaken to try to prevent VTE in children. In this study, we sought to review the different published guidelines on the prevention of VTE in hospitalized children.

METHODS

We searched MEDLINE (OvidSP) for studies from inception of the database until September 2016. With a medical research librarian, we developed, refined, and performed the search. We searched for VTE AND prevent* AND (child* OR pediatr*) AND (algorithm* OR protocol* OR guideline*). We also hand searched our personal lists and references of eligible studies. From the list of articles, we identified those that reported on a guideline for the prevention of DVT in children. Salient characteristics of each guideline including target population, risk factors considered, intervention, compliance, and frequency of DVT and bleeding were abstracted from the full text of the article (**Tables 1** and **2**).

RESULTS

We obtained a total of 55 articles from our literature search. Of these, four articles fulfilled our criteria (10–13). An additional article was added from our personal list (14).

Braga and Young (10)

Braga and Young proposed a pediatric thromboprophylaxis flow chart based on a survey they conducted among PICUs in England and Wales, review of their cases of DVT and a formal literature review. They recommended that all children in their PICUs be assessed daily for VTE while immobile. For this, they created a risk assessment table patterned after one that is used in adults. Risk factors included CVC, pregnancy, congenital heart disease, obesity, malignancy, major trauma, massive burns, oral contraceptive pill, prolonged surgery, long term steroids, and mechanical ventilation. In low-risk children without any risk factors, early mobilization and adequate hydration were

TABLE 1 | Characteristics of published guidelines for thromboprophylaxis in children.

Reference	Target population	Risk categories	Criteria	Interventions
Braga and Young (10)	Children in the pediatric intensive care unit (PICU)	Low risk At risk	Immobility ≥1 additional risk factor for VTE	Early mobilization and adequate hydration Mechanical prophylaxis, pharmacologic prophylaxis to be considered for children with burns
Raffini et al. (11)	Children ≥14 years old	Low risk At risk High risk	No risk factors for VTE ≥1 risk factor (excluding immobility) or immobility without other risk factors for VTE Immobility with ≥1 additional risk factor for VTE	Early ambulation Mechanical prophylaxis Mechanical and (strong consideration) pharmacologic prophylaxis
Hanson et al. (12)	Children admitted to the PICU after trauma	Low risk of VTE High risk of VTE with high risk of bleeding High risk of VTE with low risk of bleeding	<13 years old and ≤3 risk factors for VTE ≥13 years old or <13 years old with ≥4 risk factors for VTE and ≥1 risk factor for bleeding ≥13 or <13 years old with ≥4 risk factors for VTE and no risk factor for bleeding	None Mechanical prophylaxis and surveillance ultrasound Mechanical and pharmacologic prophylaxis
Meier et al. (14)	Children 10–17 years old	Low risk Moderate risk High risk	No risk factors for VTE ≥1 risk factor for VTE (excluding immobility) or immobility with ≤1 risk factor for VTE Immobility with ≥2 risk factors	Early ambulation and mitigation of risk factors Mechanical prophylaxis Mechanical and pharmacologic (to be considered) prophylaxis
Mahajerin et al. (13)	Children >12 years old	Low risk Moderate risk High risk	No risk factors for VTE Combinations of risk factors for VTE determine moderate versus high risk	Early ambulation Mechanical prophylaxis Mechanical and pharmacologic prophylaxis

VTE, venous thromboembolism.

TABLE 2 | Summary of factors used in the stratification of risk of venous thromboembolism (VTE) in the different guidelines.

Risk factors	Braga and Young (10)	Raffini et al. (11)	Hanson et al. (12)	Meier et al. (14)	Mahajerin et al. (13)
Central venous catheter	√	√	√	√	√
Exogenous estrogen	√	√	√	√	√
Immobility	√	√	√	√	√
Inflammatory disease		√	√	√	√
Lower extremity trauma	√	√	√	√	
Obesity	√	√		√	√
Prior VTE		√	√	√	√
Infection		√		√	√
Malignancy	√		√	√	
Spinal cord injury		√	√	√	
Thrombophilia		√	√	√	
Burns	√	√			
Cardiac disease	√				√
Family history of VTE		√			√
Lower extremity surgery		√		√	
Mechanical ventilation	√				√
Nephrotic syndrome		√		√	
Pregnancy	√	√			
Admission to the intensive care unit					√
Asparaginase therapy				√	
Cardiopulmonary resuscitation			√		
Hyperosmolar therapy				√	
Inotropes			√		
Low Glasgow Coma Score			√		
Major surgery	√				
Parenteral nutrition					√
Prolonged hospital stay					√
Sickle cell disease					√
Steroids	√				

recommended. In addition to these, mechanical prophylaxis was recommended for at-risk children defined as those with any risk factor. Short-term CVCs should be removed within 24 h unless a physician documents that it should remain. Anticoagulation with LMWH should be considered for children with burns. However, a consultant had to make the decision to anticoagulate. Compliance with the protocol and frequency of DVT or bleeding were not reported.

Raffini et al. (11)

As part of a patient safety and quality improvement initiative that began in response to several adolescent and young adults with hospital-acquired lower extremity DVT and PE, Raffini et al. used local data, published adult guidelines, and expert consensus to develop institutional recommendations for VTE prophylaxis. This initiative was targeted at hospitalized children ≥14 years old. In their guideline, the mobility status played an important criterion for risk stratification. Children ≥14 years old who were mobile during their stay were considered low risk and ambulation was encouraged. Children ≥14 years who had altered mobility were assessed for additional prothrombotic risk factors (i.e., obesity, estrogen, major surgery, burns, trauma, thrombophilia, nephrotic syndrome, prior VTE, inflammatory disorders, and infection). They were considered at risk for VTE if none of the additional prothrombotic risk factors were present, and high risk if at least one additional risk factor was present. Mechanical prophylaxis was recommended for at-risk children, while children who were at high risk were recommended to receive mechanical and/or pharmacologic prophylaxis. Contraindications for pharmacologic prophylaxis were included in the guideline. Dosing strategies for anticoagulation were largely extrapolated from adult recommendations (30 mg enoxaparin twice daily for high-risk orthopedic surgery patients, and 40 mg enoxaparin daily for medical patients for those >60 kg). The recommendations also included placement of sequential compression devices in all children ≥14 years old undergoing surgical procedures >45 min duration.

Compliance with the recommendations improved from 22 to >80% over the 4-year study period. A follow-up prospective study evaluating bleeding in 89 patients who received enoxaparin reported two major bleeding events and five minor bleeding events, all in children who underwent major orthopedic surgery (15). Therefore, the risk of major bleeding in the orthopedic surgery patients was 4% (2/51) and 0% (0/38) in the remaining patients. No child developed a non-CADVT.

Hanson et al. (12)

Hanson et al. reported on a guideline for VTE prophylaxis in children admitted to the PICU after trauma. Based on the guideline, children were classified into three categories: high risk of VTE and without high risk of bleeding, high risk of VTE and with high risk of bleeding, and low risk of VTE. Risk factors for VTE were projected prolonged immobility, low Glasgow Coma Scale score, presence of CVC, spinal cord injury, complex lower extremity fracture, operative pelvic fracture, use of inotropes, cardiopulmonary resuscitation, exogenous estrogen,

chronic inflammatory state, history of previous DVT, known thrombophilia, and current malignancy. High risk of VTE was defined as age >13 years or age <13 years with four or more risk factors for VTE. Low risk of VTE was age <13 years and three or fewer risk factors for VTE. Risk factors for bleeding were intracranial bleed, solid organ injury, planned surgical intervention, or invasive procedure in the next 24 h, heparin allergy, high risk of severe bleeding, and renal failure. The presence of one or more risk factors for bleeding classified the patient as high risk of bleeding. For patients at high risk of VTE and without high risk of bleeding, pharmacologic prophylaxis with LMWH and mechanical prophylaxis were recommended. For patients at high risk of VTE and with high risk of bleeding, only mechanical prophylaxis was recommended. However, screening ultrasound for VTE had to be performed if the child was still in the PICU on hospital day 7. Therapeutic heparin was started if the ultrasound showed VTE and if the bleeding risk has diminished. Children at low risk of VTE were not recommended to receive prophylaxis nor surveillance ultrasound be performed.

The authors reported a compliance with the guideline of 93%. Of 169 children, 60 were high risk of VTE and high risk of bleeding, 16 high risk of VTE and without high risk of bleeding, and 93 low risk of VTE. A total of three (2%) children developed asymptomatic DVT detected on surveillance ultrasound. This was lower than the 5% with VTE prior to implementation of the guidelines. There were no bleeding complications.

Meier et al. (14)

Meier et al. proposed a guideline for use in hospitalized children 10–17 years old. The recommendations were developed after a thorough review of the literature. Based on the guideline, a child is considered at low risk of VTE if the child was not expected to have prolonged altered mobility and had no risk factors. A child was at moderate risk of VTE if the child was not expected to have prolonged altered mobility but had risk factor for VTE, or was expected to have prolonged altered mobility but at most one risk factor for VTE. High risk of VTE was when prolonged altered mobility was expected and with at least two risk factors for VTE. Risk factors for VTE include bloodstream infection, CVC, history of VTE, hyperosmolar state, inflammatory diseases, asparaginase, estrogen use, obesity, oncologic diagnosis, hip or knee reconstruction, nephrotic syndrome, thrombophilia, multiple lower extremity long bone fracture, complex pelvic fractures, and spinal cord injury. For the low-risk group, early ambulation was encouraged and risk factors mitigated. For the moderate-risk group, use of mechanical prophylaxis was recommended in addition to the recommendations for the low-risk group. For the high-risk group, pharmacologic prophylaxis should also be considered. Absolute and relative contraindications to pharmacologic prophylaxis were listed in the guideline. The authors did not report the compliance with the guideline nor the frequency of DVT and bleeding with the use of the guideline.

Mahajerin et al. (13)

Mahajerin et al. developed a guideline for use in hospitalized children >12 years old. For children younger than 12 years old, VTE prophylaxis was considered on an individualized basis. Based on literature review in children and adults, and statistical modeling, they ranked the association of different factors with VTE and grouped them into two tiers. Tier 1 risk factors were those that retained statistical significance in a multivariable regression model. This included prolonged immobilization, estrogen therapy, and prolonged hospital stay. Additional factors added in tier 1 were autoimmune disease with antiphospholipid antibody positivity and acute flare, dilated cardiomyopathy, atrial fibrillation, single-ventricle physiology, palliative surgical shunts, cystic fibrosis with *B. cepacia* infection, diabetic ketoacidosis, inflammatory bowel disease with acute flare, sickle cell anemia, history of VTE, known thrombophilia, and myocardial infarction in a first- or second-degree relative <50 years old. Tier 2 factors were statistically significant in the bivariate analysis but not in the multivariable regression model. This included bacteremia, obesity, chronic parenteral nutrition, initial PICU admission, mechanical ventilation, and other serious bacterial infections. The combination of these risk factors identified a child's risk group. Only ambulatory children without risk factors were included in the low-risk group. Non-ambulatory children with or without a CVC but not any other risk factor classified a child as moderate risk. Presence of any other risk factors elevated the category to high risk. In the low-risk group, only ambulation was recommended. In the moderate-risk group, mechanical prophylaxis was also recommended. Mechanical and pharmacologic prophylaxis were recommended in the high-risk group unless with contraindications. Separate lists of contraindications for mechanical and pharmacologic prophylaxis were included in the guideline.

For the first 17 months that the guideline was implemented, an average of 69% of 149 qualified patients were screened. Compliance with the guidelines was not reported. However, none of the screened patients developed VTE compared to three cases in the 12 months prior to the guidelines. No bleeding events were reported with the use of enoxaparin.

DISCUSSION

Although the rate is increasing, VTE is still far less common in children than in adults (1, 16). Thus, current recommendations for treatment of VTE in children are largely extrapolated from adult studies (17). Similarly, many of the prevention strategies discussed above were based upon adult guidelines and expert opinion, in response to adolescents who developed hospital-acquired VTE as well as a national initiative implemented in 2008 by the Joint Commission to focus attention on VTE prevention (18). In this systematic review, we identified five guidelines for the prevention of VTE in children. The guidelines were mainly targeted at adolescents and used various risk-stratification approaches. Over 20% of patients hospitalized in children's hospitals are 14 years or older and 6% are 18 years or older (11). Furthermore, hospitalized adolescents may have multiple risk factors for VTE, rivaling those of their adult counterparts. However, adolescents or young adults with hospital-acquired, non-CADVT account for a relatively small proportion of VTE in children, while the majority of thrombotic events occur in younger children and are associated

with CVC (11). Therefore, it is important to recognize that adult thromboprophylaxis guidelines are based upon the proven efficacy of anticoagulants to reduce the rate of lower extremity DVT, and not necessarily CADVT.

In a recent survey of pediatric hemostasis and thrombosis experts in North America, Badawy et al. showed that approximately one-third and one-half of their respondents reported having guidelines for pharmacologic and mechanical prophylaxis against DVT, respectively, in their hospitals (19). The majority of the respondents did not support the adoption of universal pharmacologic prophylaxis. There was significant variability on which risk factors influenced the decision to provide pharmacologic prophylaxis. Our findings are consistent with this survey. None of the published guidelines recommended universal pharmacologic prophylaxis. While age and immobility were consistent determinants of the risk of VTE across guidelines, there was significant variability in the other risk factors considered. It is interesting to note that despite being the most common cause of DVT in children, the presence of CVC was not a prominent factor in the risk-stratification approaches. This is likely related to the negative RCTs on pharmacologic prophylaxis against CADVT in children (9). In low-risk children, ambulation was the only recommended intervention. Mechanical prophylaxis was recommended for moderate risk while pharmacologic and mechanical prophylaxis were recommended for the high-risk group if there were no contraindications to pharmacologic prophylaxis. The choice of prevention strategy likely reflected the perceived safety of mechanical prophylaxis, despite its reduced efficacy compared to pharmacologic prophylaxis, in children, based on data from adults (5–7).

Randomized controlled trials are an ideal way to determine the efficacy of an intervention. However, the conduct of RCTs of thromboprophylaxis in children has been difficult. A major problem is the low numbers of clinically apparent VTE in children (9). In hospitalized children, the rate is only 34–58 cases per 10,000 admissions (1). Thousands of children and multiple centers will be needed to successfully complete an RCT that will detect a clinically significant reduction in VTE. To increase the frequency of the outcome, and thus decrease the estimated sample size, ultrasound diagnosed DVT have been recommended and used as outcomes in RCTs in adults and children (5–7, 9, 20). Because some subjects have asymptomatic DVT, using routine ultrasound in a study increases the event rate compared to using symptoms to guide which patients are evaluated for DVT. The increased event rate leads to the need for a smaller sample size to achieve the same power to detect a treatment difference. Aside from the convenience in lowering the sample size, the use of ultrasound diagnosed DVT as outcome minimizes the risk of ascertainment bias in detecting DVT by physical examination alone (20). Venography was frequently used to diagnose DVT in adult studies (21). Because of difficulties in performing venography in children, its use has been supplanted by ultrasonography. Some practitioners question the use of ultrasound-diagnosed DVT as outcome. In a survey of pediatric critical care physicians, most stated that asymptomatic DVT diagnosed by radiologic imaging alone are not clinically significant (22). Long-term outcomes are needed to determine whether asymptomatic DVT is a clinically relevant outcome in children (23).

If RCTs will be performed to determine the efficacy of prophylaxis against DVT in children, innovative study designs are needed. For example, a risk-stratified approach that mirrors the published guidelines may need to be incorporated into the study design. Bayesian study design with adaptive randomization is a potential alternative to determine the differential effect of mechanical and/or pharmacologic prophylaxis (24). This design has the advantage of dropping treatment arms that are likely to be futile then direct subjects to promising treatment. Sample size decreases because more subjects are enrolled in fewer treatment arms. Quasi-experimental designs, such as stepped wedge trials, should also be considered. Such a design can enhance participation because each center is guaranteed to get the intervention at some point (25).

In lieu of RCTs, other sources of evidence are needed to inform our practice on the prevention of VTE in children. Guidelines can provide some of this information because their consistent use can minimize variability in practice and increase the replicability of results (26). However, it is crucial that data are collected accurately. Of the five guidelines reviewed, only two provided data on compliance and three provided data on the frequency of DVT and bleeding (11–13). Each center on its own is unlikely to obtain sufficient numbers of children to prove any statistically significant difference. Meta-analysis of data from each of the centers might be a useful approach to strengthen conclusions about the efficacy of VTE prevention strategies. It may be possible to perform such analysis because of similarities in the guidelines, particularly those of Raffini et al., Meier et al., and Mahajerin et al. (11, 13, 14). Comparable historical controls would be required to make the analysis robust. This would require careful thought to identify appropriate controls. Finally, the Solutions for Patient Safety network is collecting high-quality data on patients with VTE and strategies are being developed to reduce VTE (8). This quality improvement initiative has the potential to identify effective VTE prevention strategies.

In conclusion, evidence is lacking on the right approach to the prevention of VTE in children. RCTs, which are the gold standard, are very difficult to conduct. Innovative designs are needed to successfully complete these RCTs. Guidelines have been developed despite the paucity of evidence to help with patient management. These guidelines can be a source of valuable information to inform our practice.

AUTHOR CONTRIBUTIONS

EVF and LR conceived and designed, collected, analyzed, and interpreted the guidelines, and co-wrote the first draft of the manuscript. Both authors revised the manuscript for important intellectual content, approved this version of the manuscript, and took full responsibility for the manuscript.

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