Venous Thromboembolism in Hospitalized Adolescents: An Approach to Risk Assessment and Prophylaxis

abstract

BACKGROUND: Pediatric hospital-acquired venous thromboembolism (VTE) is an increasingly prevalent and morbid disease. A multidisciplinary team at a tertiary children's hospital sought to answer the following clinical question: “Among hospitalized adolescents, does risk assessment and stratified VTE prophylaxis compared with no prophylaxis reduce VTE occurrence without an increase in significant adverse effects?”

METHODS: Serial literature searches using key terms were performed in the following databases: Medline, Cochrane Database, CINAHL (Cumulative Index to Nursing and Allied Health), Scopus, EBMR (Evidence Based Medicine Reviews). Pediatric studies were sought preferentially; when pediatric evidence was sparse, adult studies were included. Abstracts and titles were screened, and relevant full articles were reviewed. Studies were rated for quality using a standard rating system.

RESULTS: Moderate evidence exists to support VTE risk assessment in adolescents. This evidence comes from pediatric studies that are primarily retrospective in design. The results of the studies are consistent and cite prominent factors such as immobilization and central venous access. There is insufficient evidence to support specific prophylactic strategies in pediatric patients because available pediatric evidence for thromboprophylaxis efficacy and safety is minimal. There is, however, high-quality, consistent evidence demonstrating efficacy and safety of thromboprophylaxis in adults.

CONCLUSIONS: On the basis of the best available evidence, we propose a strategy for risk assessment and stratified VTE prophylaxis for hospitalized adolescents. This strategy involves assessing risk factors and considering prophylactic measures based on level of risk. We believe this strategy may reduce risk of VTE and appropriately balances the adverse effect profile of mechanical and pharmacologic prophylactic methods.
admissions from 2001 to 2007. Rates in pediatric trauma patients are even higher (retrospective studies of high-risk cases demonstrate rates of 60 to 100 per 10,0001,3,6; 1 small prospective study reported 620 per 10,0006). Consequences of VTE for hospitalized pediatric patients are significant, including pulmonary embolism (16%–20% of pediatric patients with VTE), post-thrombotic syndrome (at least 20% of children with DVT), chronic pulmonary insufficiency, pulmonary hypertension, and mortality (9% among pediatric pulmonary embolism cases).7,8

Given this background of increasing VTE incidence, regulatory bodies such as the Joint Commission and the Surgeon General have launched initiatives to increase awareness of VTE.9,10 There are well-established guidelines for risk stratification and prophylaxis in the adult population, but there is a paucity of similar protocols in children. Such guidelines are particularly important as pediatric hospitals care for growing populations of medically complex children who may be at higher risk of VTE.

Studies of age and VTE incidence in hospitalized pediatric patients have demonstrated a bimodal distribution, with peaks in neonatal and in adolescent populations.7,10,11 The increasing risk after age 10 correlates with full maturation of the hemostatic system.12 Because of heterogeneity in risk factors between these 2 peaks, we chose to focus on the second peak of pediatric VTE incidence, defined as ages 10 to 17 years.

METHODS
Pediatric faculty representing hematology, critical care, orthopedics, general/trauma surgery, and hospital medicine along with a methodologist from our institution formed a multidisciplinary taskforce. The aim of this taskforce was to review the available literature and develop care recommendations for VTE prophylaxis in hospitalized patients between ages 10 and 17 years of age. The primary PICO (population intervention comparison outcome) question addressed was:

P (Population): Among hospitalized adolescents
I (Intervention): does risk assessment and stratified VTE prophylaxis
C (Comparison): compared with no prophylaxis
O (Outcome): reduce VTE occurrence without an increase in significant adverse effects?

As the evidence review progressed, additional questions were posed by the reviewers regarding the definition of immobility and specific rates of adverse events with various prophylactic strategies. When pediatric evidence was sparse, adult studies were included. In addition, articles identified by members of the team and relevant articles from reference lists were considered. Our search methods are available as an online Supplemental Appendix.

The LEGEND (Let Evidence Guide Every New Decision)13 system (Table 1) was selected for evidence evaluation because it was developed to provide flexibility in the evaluation of bodies of literature regardless of study designs or quality and quantity of literature to answer a clinical question. The body of evidence on risk factors was expected to comprise weak study designs, and the body of evidence on prophylaxis was expected to be nonpediatric indirect evidence. The multidisciplinary taskforce discussed the evidence and made consensus recommendations.

RESULTS
The search strategy identified 832 articles (35% pediatric). Full text was reviewed for 250 articles (37% pediatric), and 44 are cited for the final review (64% pediatric). The LEGEND grade of the body of evidence to support risk assessment is moderate. Risk assessment is based on pediatric studies with weak study design (primarily retrospective studies); however, the results among the many studies

<table>
<thead>
<tr>
<th>Grade</th>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td>High</td>
<td>Sufficient number of high-quality studies with consistent results</td>
<td>Further research is unlikely to change our confidence in the answer to the clinical question.</td>
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<tr>
<td>Moderate</td>
<td>A single well-performed study, or multiple studies of lesser quality or with some uncertainty</td>
<td>Further research is likely to have an important impact on our confidence in the precision of the answer to the clinical question and may even change the answer itself.</td>
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<tr>
<td>Low</td>
<td>Studies with insufficient quality including case reports, case studies, general reviews, and local consensus</td>
<td>There is published and/or local consensus, but little or no research, to answer the clinical question. Further research is likely to have an important impact on the answer.</td>
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<tr>
<td>Grade not assignable</td>
<td>Insufficient design or execution, too few studies, inconsistent results, and lack of consensus</td>
<td>There is insufficient evidence and lack of consensus to answer the clinical question.</td>
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TABLE 1 Grading the Body of Evidence13
**VTE Risk Factors**
- Blood stream infection
- Central Venous Catheter (including non-tunneled, tunneled and PICCs)
- History of venous thrombosis
- Hyperosmolar state (serum osmolality >320 mOsm/kg)
- Inflammatory diseases (e.g., IBD, SLE)
- Medications: asparaginase, estrogen use (within past 2 months)
- Obesity (BMI > 95th percentile for age)
- Oncologic diagnosis
- Orthopedic procedures: hip or knee reconstruction
- Nephrotic syndrome
- Thrombophilia – known, or family history of clots
- Trauma: >1 lower extremity long bone fracture, complex pelvic fractures, spinal cord injury

**Contraindications to Mechanical Prophylaxis**
- DVT, suspected or existing (can use GCS)
- Extremity to be used has acute fracture
- Extremity to be used has PIV access
- Skin conditions affecting extremity (e.g., dermatitis, burn)
- Unable to achieve correct fit due to patient size

**Contraindications to Anticoagulation**
- **Absolute:**
  - Bleeding disorder, known or tendency
  - Hemorrhage, evidence of or high risk of
  - Platelet count unable to be sustained > 50,000/mm³
- **Relative:**
  - Intracranial mass
  - Lumbar puncture or epidural catheter removal in prior 12 hours
  - Neurosurgical procedure
  - Pelvic fracture within past 48 hours
  - Uncontrolled hypertension

**Algorithm, risk category assessment and prophylaxis for VTE in children.**

**Start:** Hospitalized patient age 10 to 17 years

**Exclude patients:**
- 18 years and older (eligible for assessment and treatment by adult guideline)
- With current VTE

**Altered mobility > 48 hrs?**

**Other risk factors?**

**# of other risk factors?**

- **Low**
- **Moderate risk**
- **High risk**

**Anticoagulation contraindicated?***

**Intervention:**
- Encourage early ambulation
- Mitigate risk factors

**AND** Mechanical prophylaxis
- SCD (preferred)** and/or GCS
- Make efforts to achieve 18 hours of daily use

**AND** Consider pharmacologic prophylaxis

**Reassess risk at 48 to 72 hours of hospitalization**
are consistent. The LEGEND grade of the body of evidence to support thromboprophylaxis in pediatrics is low. The thromboprophylaxis recommendations are based on adult studies and local consensus.

**Risk Factors**

**Age**

Many pediatric studies observed a bimodal age distribution in hospital-acquired VTE, with peaks occurring in infancy and adolescence.\(^7\)\(^,\)\(^10\) Increasing older age was a consistent risk factor in multiple pediatric studies.\(^3\)\(^,\)\(^4\)\(^,\)\(^14\)\(^–\)\(^18\)

**Anesthesia**

Adult studies have shown that during anesthesia, there is loss of normal muscle tone and a decrease in venous pump action, resulting in dilated veins and slowed venous blood flow, increasing VTE risk during anesthesia.\(^19\)

**Altered Mobility**

The association between immobility and VTE is strongly demonstrated in the adult population and supported by a pediatric retrospective case-control study with separate cohort validation,\(^20\) in which prolonged immobilization (>72 hours) was found to be the most significant factor predicting VTE risk. In addition to this study, a number of factors identified in other pediatric retrospective studies are thought to confer risk of VTE due to their contribution to altered mobility. These factors include prolonged hospitalization, increasing severity of injury, mechanical ventilation, and ICU admission.\(^3\)\(^–\)\(^5\)\(^,\)\(^7\)\(^,\)\(^14\)\(^–\)\(^18\)\(^,\)\(^21\)\(^–\)\(^24\)\(^,\)\(^26\)\(^–\)\(^28\)

**Central Venous Line**

The presence of a central venous access line is highly correlated with increasing VTE risk in multiple retrospective pediatric studies.\(^3\)\(^–\)\(^5\)\(^,\)\(^10\)\(^,\)\(^15\)\(^,\)\(^17\)\(^,\)\(^20\)\(^–\)\(^22\)

**Other Risk Factors**

One prospective and multiple retrospective studies, including 2 with a control comparison,\(^22\) evaluating risk factors for VTE in pediatric trauma, surgery, neurosurgery, orthopedic surgery, and medical patients showed consistency.\(^3\)\(^–\)\(^5\)\(^,\)\(^10\)\(^,\)\(^14\)\(^–\)\(^18\)\(^,\)\(^21\)\(^–\)\(^24\)\(^,\)\(^26\)\(^–\)\(^28\)

Key risk factors identified in these studies, in addition to those related to altered mobility, were total parental nutrition, estrogen use, obesity, bloodstream infection, surgery, inflammatory disease, specific injuries (such as spinal cord, traumatic brain injury, pelvic fracture and long bone fracture injuries), specific procedures (such as spinal procedures, cranial procedures, and open reduction and internal fixation of a lower extremity long bone), increasing age, and family history of thrombophilia. In 1 retrospective study, patients with nephrotic syndrome had a markedly increased rate of hospital-acquired VTE, as did patients with oncologic diagnoses.\(^10\) Specifically, leukemia was the most frequent diagnosis associated with hospital-acquired VTE.\(^10\)

Other risk factors were identified from adult studies and local consensus: asparaginase therapy, hyperosmolar state, and total hip or knee replacement.\(^29\)\(^,\)\(^30\)

**Combined Effect**

Some studies demonstrated the combined effect of multiple risk factors. For example, the combination of mechanical ventilation, systemic infection and hospitalization ≥5 days gave a post-test probability of VTE of 3.1% (compared with pretest probability of 0.35%).\(^7\) Also, a prospective study noted an increase in odds of VTE development for each additional central venous catheter placed (7.9-fold increase; \(P = .005\)), for each additional risk factor present (threelfold increase; \(P = .009\)), and for increasing severity of injury (1.3-fold increase; \(P = .03\)).\(^5\)

Lastly, a retrospective study noted a fourfold increase of hospital-associated VTE in patients with at least 4 complex chronic conditions compared with patients with only 1 chronic condition.\(^10\)

**Timing of VTE Risk**

In a study by Sharathkumar et al (2012), the majority of VTE events were diagnosed within a week of hospitalization (mean of 7 days and median of 3 days).\(^20\) The median time to VTE diagnosis was also similar in Branchford et al (2012) at 7 days.\(^7\)

**Mechanical Prophylaxis**

There were no pediatric studies of mechanical prophylaxis. Cochrane meta-analyses of adult patients support the efficacy of mechanical prophylaxis in patients at risk for VTE. The relative risk (RR) of DVT in patients treated with mechanical methods compared with no treatment ranges from RR = 0.31 (95% confidence interval [CI] 0.19–0.51) in hip fracture patients\(^31\) to RR = 0.55 (95% CI 0.34–0.99) in trauma patients.\(^32\) Another large meta-analysis of hospitalized adult patients found that intermittent pneumatic compression was as effective as pharmacologic prophylaxis (with RR = 0.4) but with a decreased bleeding risk. It also showed efficacy in reducing the risk of pulmonary embolism (PE) with RR = 0.48.\(^33\)

In a small randomized control trial in adults, the use of intraoperative sequential compression device (SCD) has been shown to decrease venous stasis.\(^34\) These data support our local surgical consensus to use SCD in patients having surgery lasting at least 60 minutes.
An adult study comparing SCD to graduated compression stockings suggests SCD have superior efficacy in preventing DVT (RR = 0.48).35

Pharmacologic Prophylaxis

Multiple adult studies support the benefit of heparin in reducing DVT. The RR of DVT in patients treated with heparin compared with no treatment is 0.51 (95% CI 0.41–0.63; P < .0001)36 to 0.60 (95% CI 0.50–0.71).31 Low molecular weight heparin (LMWH) may have a slight advantage to unfractionated heparin because RR ranged from 0.68 to 0.9 in 3 meta-analyses, with significance demonstrated in 2 of the 3.31,32,36

Head-to-head comparisons of pharmacologic and mechanical prophylaxis in trauma patients show a possible slight advantage of pharmacologic prophylaxis in preventing DVT [RR = 0.48, 95% CI 0.25–0.95].32

At this time, there is insufficient evidence to recommend aspirin as a prophylactic measure.29,37,38

Efficacy of Combined Modalities

Meta-analyses of adult studies show that combining mechanical prophylaxis and pharmacologic prophylaxis lowers the overall risk of VTE compared with either single modality with RR ranging from 0.31 to 0.5 in 4 types of comparisons, all statistically significant.32,33,39

Safety and Harm

Adverse event rates of SCD are low and generally minor. They include discomfort, intolerance, and skin abrasions. Discomfort may lead to decreased adherence.31

A meta-analysis of pediatric studies on the safety of LMWH suggests a rate of “clinically relevant” bleeding with LMWH of ~2.3%; all events were in 1 study that used twice-a-day dosing.50 A recent prospective observational study of children (n = 89) with prophylactic enoxaparin calculated a similar rate of major bleeding (2.2%) and minor bleeding (5.6%).41 Major bleeding, as defined by the International Society of Hemostasis and Thrombosis, includes fatal bleeding, overt bleeding with hemoglobin drop of ≥2 g/dL in 24 hours, bleeding into a critical organ (brain, lung, retroperitoneal), or bleeding requiring surgical intervention. Minor bleeding is defined as overt or macroscopic bleeding that does not meet criteria for major bleeding. Both major bleeding events occurred in orthopedic patients.41

The American Society of Regional Anesthesia recommends waiting 2 hours after atraumatic epidural catheter placement or removal and 12 hours after possibly traumatic catheter placement or removal before starting LMWH, to avoid the risk of hematoma.42

**DISCUSSION**

On the basis of the evidence described here, we developed the following recommendations and algorithm (see Fig 1) for VTE risk assessment and prophylaxis in children aged 10 to 17 years. Age 10 was selected based on the VTE risk conferred by adolescence.

These recommendations are meant to be a general guide for the conscientious clinician and should not replace individual clinical judgment.
Recommendations

1. It is recommended that patients ages 10 to 17 years who are expected to have a surgical procedure lasting ≥60 minutes be started at induction of anesthesia on a SCD for prophylaxis of VTE unless there are contraindications to mechanical prophylaxis (Table 2).19,23,34

2. It is recommended that all patients ages 10 to 17 years be assessed for VTE risk factors (see Table 3) and, on the basis of that assessment, assigned to a risk category of low, moderate, or high (see Table 4). They should be assessed:
   a. at the time of inpatient admission, and
   b. reassessed at 48 to 72 hours of hospitalization.7,20

3. It is recommended that VTE prophylaxis be administered based on risk category (see Table 5) as soon as feasible but within 24 hours of assessment, unless there are contraindications.

4. It is recommended, if planning to initiate pharmacologic prophylaxis31,32,36,39–41 in surgical patients, to seek surgeon input regarding bleeding risk before initiation (Table 6 lists contraindications to pharmacologic intervention).

These recommendations are summarized in the algorithm (Fig 1).

LIMITATIONS

The strength of these recommendations are limited by the lack of good quality pediatric evidence to answer the clinical question. Reliance on retrospective studies for the assessment recommendations may have introduced selection bias. Reliance on expert consensus of the multidisciplinary taskforce for the prophylaxis recommendations was required, as adult studies were the only available published evidence.

CONCLUSIONS

At this time, there is sufficient evidence to assess and stratify risk of VTE in pediatric patients. There is minimal pediatric evidence to support specific prophylactic strategies. We believe a stratified approach to prophylaxis based on risk may reduce the risk of VTE. Providers should carefully balance potential benefits and risks (including known contraindications) of prophylaxis before implementing a specific therapy.

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