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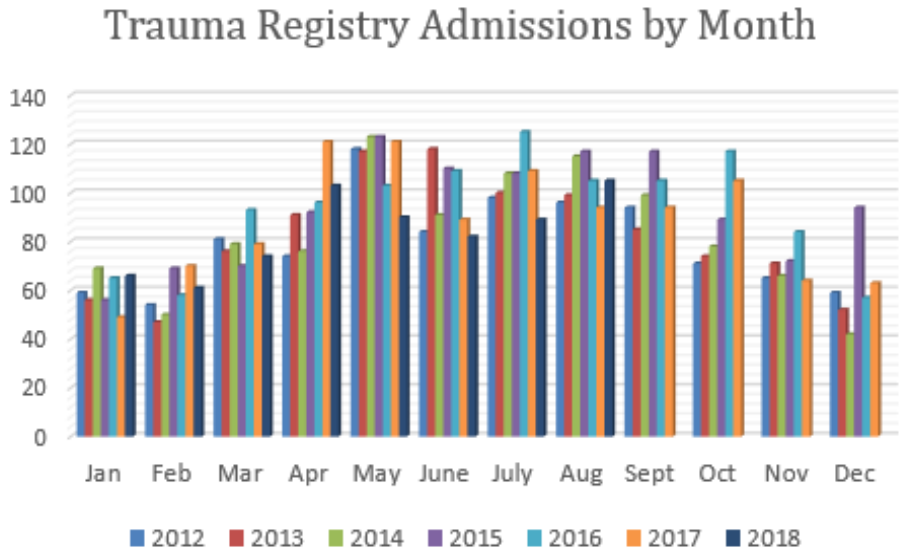
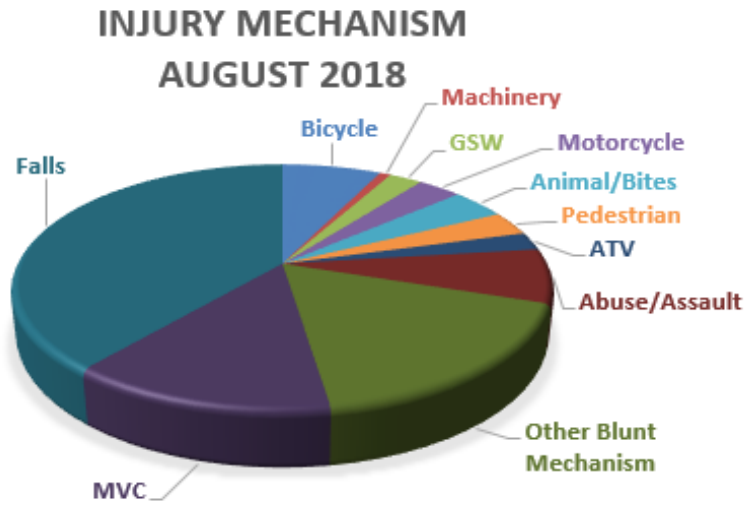
Monroe Carell Jr. Children's Hospital at Vanderbilt

Pediatric Trauma Service's IEP

AUGUST 2018 REGISTRY DATA





INSIDE THIS ISSUE

ELEVATING TRAUMA PI CONCERNS

- For any patient quality concerns or system issues related to our trauma population, please feel free to contact Amber Greeno.
- 615-936-7074 (office)
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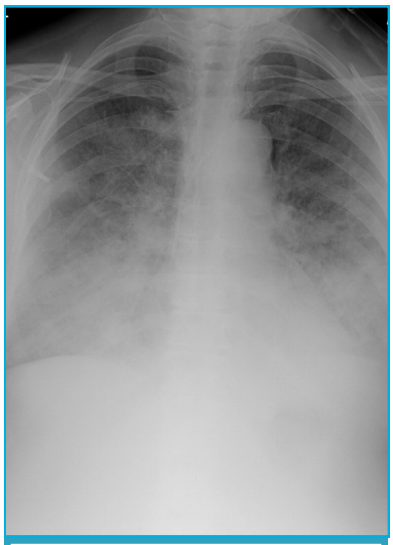
TRANSFUSION-RELATED ACUTE LUNG INJURY



HIGHLIGHTS FROM JENNIFER ANDREW'S "TRALI" TALK

* There is nothing from the blood bank that we send to test to actually confirm the diagnosis of TRALI so it is completely at the bedside.
* About 80% of patients will improve within just a couple of days with supportive care.
* In 2006 after 25 fatal cases of TRALI, the FDA instituted the practice of not allowing donors likely to have HLA antibodies (i.e. women who have been pregnant) to donate plasma in this country.
* This measure dropped the number of fatal cases to 16 in 2008.
* In the case presented, the patient developed TRALI from pRBCs, which is the trend we are seeing across the country.

Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-associated morbidity and mortality (2). Because no single laboratory test is pathognomonic for TRALI, the diagnosis is made based principally on clinical and radiographic findings.

The radiographic features of TRALI are nonspecific and typically begin as patchy infiltrates that evolve into bilateral alveolar and interstitial infiltrates and often result in a classic white-out of the lung.

The most frequent clinical findings included respiratory distress, hypoxemia, acute pulmonary edema, hypotension, tachycardia, and fever. All symptoms start within 6 hours and most occur within 1 to 2 hours of the transfusion of a plasma-containing blood product. In fact, many cases begin within minutes of the start of a transfusion. The pulmonary edema may begin in dependent areas of the lung, but over several hours will typically involve the entire lung field. Hypotension, when present, does not typically respond to intravenous fluid infusion.

Transfusion-related acute lung injury is likely a syndrome with a spectrum of clinical presentation ranging from mild to severe. The mild cases likely present with dyspnea and fever. The severe cases likely have hypoxemia, pulmonary edema, and hypotension, in addition to the dyspnea and fever.

The most frequently implicated blood products are whole blood, packed RBCs, FFP, and platelet concentrates or apheresis platelets.

All patients with TRALI require supplemental oxygen and more than 70% of patients require mechanical ventilation. The physiological abnormalities and pulmonary infiltrates usually resolve over 4 days in approximately 80% of patients. 20% of patients have slower resolution, but resolution is generally complete, even in these patients. Mortality has been reported to be in the range of 6% to 14%.

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI) VERSUS TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)

Clinical Feature	TRALI	TACO
Body Temperature	+/- Fever	Normal
Blood Pressure	+/- Hypotension	+/1 Hypertension
Respiratory	Acute dyspnea	Acute dyspnea
Neck Veins	Unchanged	May be distended
Auscultation	Rales	Rales +/- S3
CXRY	Diffuse b/l infiltrates	Diffuse b/l infiltrates
Ejection Fraction	Normal	Decreased
Fluid Balance	Neutral or -	+
Response to Diuretic	Inconsistent	Significant improvement
WBC	+/- transient	Unchanged
BNP	<250 pg/ml	>1200 pg/ml

VENOUS THROMBOEMBOLISM IN PEDAITRIC TRAUMA

Hospital-acquired venous thromboembolism (VTE) in pediatrics is a major source of comorbidity causing increased length of stay (LOS) and is associated with excess inpatient costs ranging from $12,000 to $28,000 per hospitalization (5). The incidence of VTE in injured children is higher than in the general hospitalized pediatric population, ranging from 0.02% to 1% for children hospitalized after trauma, and as high as 3–6% in critically ill injured children (1). Given the rising incidence of VTE in children and the resultant morbidity and excess cost, there is growing impetus for hospitals to institute local pediatric guidelines on VTE prophylaxis, particularly in high-risk populations, such as those hospitalized after trauma.

The frequency of VTE in children remains lower than adults, but is increasingly diagnosed in hospitalized pediatric patients, presumably from improvements in the care of critically ill children, increased awareness, and better detection methods. Risk factors associated with VTE in pediatric trauma patients have been identified and include older age, higher Injury Severity Scores (ISS), major vascular injury, central venous catheter use, poor perfusion, inotropic support, blood product transfusions, immobility, and spinal cord injury.

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 (3). 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. 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.

Interestingly, one study's data suggested that while the presence of CVCs is strongly associated with DVT, the removal of these lines does not eliminate this risk (4). This would suggest that vessel trauma from line placement is a contributing factor; careful consideration should be given to the need for central access, and ultrasound guidance should be available to avoid multiple injuries to the vessel; the catheter is not the sole driver of DVT, as 33% of patients who had a line removed had radiographic evidence of patent vessel between line removal and DVT diagnosis.

Eastern Association for the Surgery of Trauma (EAST) and the Pediatric Trauma Society (PTS) VTE Prophylaxis Management Recommendations
1. In children hospitalized after trauma who are at low risk of bleeding, we conditionally recommend pharmacologic prophylaxis be considered for those >15 y old and in younger post-pubertal children with ISS >25. We conditionally recommend against the use of routine pharmacologic prophylaxis in prepubertal children, even with ISS >25.
2. In children hospitalized after trauma, we conditionally recommend mechanical prophylaxis be considered for those >15 y old and in younger post-pubertal children with ISS >25 versus no prophylaxis or in addition to pharmacologic prophylaxis .
3. In children hospitalized after trauma, we conditionally recommend against active surveillance for VTE with ultrasound compared with daily physical examination alone for earlier detection of VTE.

HIGHLIGHTS FROM TRAUMA PM&I DISCUSSION ON VTE

Patient AS was reviewed and the patient's extensive occlusive thrombus in the left lower external iliac vein prompted the following discussion points:

* The Pediatric Hematologist present in the meeting stated there was variable practices across the country regarding the use of anti-coagulants for the management of VTEs.
* For the most part, the placement of inferior vena cava (IVC) filters has fallen out of favor among pediatric providers.
* In the PICU, Dr. Wendorf explained that once a significant thrombus event is identified, Hematology is consulted and if it is a medical patient without significant risk of bleeding, the decision is made between the initiation of Heparin or Lovenox. If it is a surgical patient, the surgical team is also involved in the decision making.
* When weighing the risks versus benefits of anticoagulation medications, the Pediatric Hematologist said sometimes it is appropriate to do nothing except simply pull the line when the associated limb is not threatened.
* NSGY stated that they recommend not anticoagulating their traumatic brain injury patients unless you must.

REVISED PEDIATRIC TRAUMA ACTIVATION CRITERIA

LEVEL I

Airway/Breathing
* Any intubated patient
* Unstable airway: artificial airway, being bagged, airway obstruction
* Significant facial or neck injury causing airway compromise

Breathing
* Respiratory distress/ compromise: increased work of breathing

Circulatory
* Age-specific hypotension: SBP <70 mm Hg + (2 x age in years)
* Cardiac arrest/CPR (in field or en route)
* Blood transfusion en route
* Significant blood loss or hemorrhage
* Penetrating injury (head, neck, torso)
* Excludes any penetrating injury isolated to the eye
* Limb threatening injuries:
* Amputation (near/complete), degloving, crush injury proximal to wrist/ ankle
* Pulseless extremity with duskiness, cyanosis, or paralysis

Disability
* GCS ≤ 8 or "P" or "U" or deteriorating by 2, with mechanism attributed to trauma
* Paralysis or quadriplegia

Other
* Burns ≥15% TBSA combined with other trauma/injury
* PED physician discretion

Full Trauma Team Response- Trauma Attending/Fellow (team leader), Trauma Resident, PED Attending/ Fellow, PED Resident, RN (2), Paramedic (1), PCT, RT, Social Work, Radiology

LEVEL II- SCENE

Airway
* Sub-Q emphysema of chest and above

Breathing
* NRB necessary to maintain SaO2 >93% with mechanism attributed to trauma

Circulatory
* Controlled arterial bleeding, stable VS
* Two or more femur/hurmerus fractures
* Pelvic or Femur fracture with significant mechanism
* Amputation (near/complete), degloving, crush injury distal to wrist/ankle excluding digits
* Penetrating injury to the extremity excluding digits

Disability
* GCS 9-13 or "V" (combative, disoriented)
* Open or depressed skull fracture
* Closed head injury with seizure activity or
* Loss of consciousness >5 minutes

Other:
* Suspected intra-abdominal injury with mechanism attributed to trauma
    * Abdominal wall bruising: seat belt sign or handlebar bruise
    * Abdominal pain/ tenderness with mechanism attributed to trauma
* MVC with: rollover, ejection, death of passenger, significant damage/intrusion, or spider windshield
* MCC, ATV with rollover, ejection
* Fall >20 feet (2nd story)
* Struck, dragged, or run over by vehicle
* Burns 10-15% TBSA combined with other trauma/injury or high-voltage burns
* PED physician discretion

Partial Trauma Team Response: Trauma Resident or Trauma NP/PA, PED Attending/Fellow (team leader), PED Resident, RN (2) or RN (1) with Paramedic (1), PCT, RT, Social Work

LEVEL II- TRANSFER

Airway

* Sub-Q emphysema of chest and above

Breathing

* Pneumo/hemothorax
* NRB necessary to maintain SaO2 >93% with mechanism attributed to trauma

Circulatory

* Controlled arterial bleeding, stable VS
* Bilateral femur fractures
* Complex pelvic fractures
* Amputation (near/complete), degloving, crush injury distal to wrist/ankle excluding digits
* Penetrating injury to the extremity excluding digits

Disability

* GCS 9-13 or "V" (combative, disoriented)
* Open or depressed skull fracture
* Stable EDH/SDH/SAH
* C-spine or spinal cord injury without or resolved paralysis

Other:

* Suspected or confirmed intra-abdominal injury with mechanism attributed to trauma
    * Abdominal wall bruising: seat belt sign or handlebar bruise
    * Abdominal pain/ tenderness with mechanism attributed to trauma
    * Confirmed intra-abdominal injury
* Burns 10-15% TBSA combined with other trauma/injur*y or high-voltage burns*
* PED physician discretion

Partial Trauma Team Response: Trauma Resident or Trauma NP/PA, PED Attending/Fellow (team leader), PED Resident, RN (2) or RN (1) with Paramedic (1), PCT, RT, Social Work

Level III

Other

* Trauma patients not meeting above criteria including patients immobilized with no significant injury
* Burns <10% TBSA combined with other trauma/injury
* Amputation (near/complete), degloving, crush injury off digits
* Penetrating injury to digits

Partial Trauma Team Response: PED Attending/Fellow, PED Resident, RN (1), PED PCT

Burn Alert

Other

* Any 2nd or 3rd degree burn with ≥10% TBSA without trauma mechanism
* Any intubated burn, smoke inhalation, or inhalation injury

Burn Team Response: Burn Resident or Burn NP, PED Attending/Fellow (team leader), PED Resident, RN (2) or RN (1) with Paramedic (1), PCT, RT, Social Work

**Burns will only be paged out as trauma activations if there is an associated or suspected injury.*
**Level II's now have two separate criteria depending on if it is a SCENE versus TRANSFER.*
**Level II TRANSFER criteria mainly removes mechanism criteria due to most hospitals completing radiology studies prior to transfer.*

NPO GUIDELINE DEVELOPMENT PROCESS

* First addressed at our Trauma Operations meeting.
* Dr. Jill Kilkelly investigated other pediatric hospital practices before discussing with her Pediatric Anesthesia Division.
* Her and her colleagues came up with a consensus about all aspects.
* Those suggestions were vetted through both Trauma and the PICU teams.
* The new guidelines are being sent forward into a Standard Operating Procedure.
* Inquiring as to whether or not this can be added as an EPIC order set.

CHANGES IN NPO GUIDELINES

The new NPO Guidelines for G/J feeds in intubated/non-intubated pts are as follows:

* Tube feeds (any location in GI tract) **in intubated** (cuffed endotracheal tubes) **patients, including cuffed tracheostomy: No wait time, keep feeds running until time of operation.**
    * Note one caveat: For intubated/trached patients **coming to the OR for an airway evaluation**, tube feeds in any location must be stopped 6 hrs prior. This is because the protective airway will be actively removed, as part of the eval, leaving it unsecured and a significant aspiration risk if tube feeds going until time of operation.
* **G-tube & post-pyloric tube feeds are considered equivalent in non-intubated patients: Stop feeds 6 hours prior to time of operation**.
* **Jejunal tube feeds** in nutritionally sensitive patients, ie trauma and burn patients or chronic oncology patients, **that are non-intubated**, with **a functional iv**: No wait time, keep feeds running until time of operation
    * Note: For jejunal feeds running via a **naso-jejunal feeding tube** (ie. not a surgically placed jejunal feeding tube) – primary team will order an xray/KUB documenting location of tube, to be performed the AM of operation, to assure no migration of a tube to proximal gi tract.
* For all types of feeding tubes, please plan to physically stop the feeds as pt is rolled down to OR. We agree no need for intraop feedings, for relatively short time in the actual OR.

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Prophylaxis against venous thromboembolism in pediatric trauma: A practice management guideline from the Eastern Association for the Surgery of Trauma and the Pediatric Trauma Society

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BACKGROUND: Despite the increasing incidence of venous thromboembolism (VTE) in hospitalized children, the risks and benefits of VTE prophylaxis, particularly for those hospitalized after trauma, are unclear. The Pediatric Trauma Society and the Eastern Association for the Surgery of Trauma convened a writing group to develop a practice management guideline on VTE prophylaxis for this cohort of children using the Grading of Recommendations Assessment, Development, and Evaluation framework.

METHODS: A systematic review of MEDLINE using PubMed from January 1946 to July 2015 was performed. The search retrieved English-language articles on VTE prophylaxis in children 0 to 21 years old with trauma. Topics of investigation included pharmacologic and mechanical VTE prophylaxis, active radiologic surveillance for VTE, and risk factors for VTE.

RESULTS: Forty-eight articles were identified and 14 were included in the development of the guideline. The quality of evidence was low to very low because of the observational study design and risks of bias.

CONCLUSIONS: In children hospitalized after trauma who are at low risk of bleeding, we conditionally recommend pharmacologic prophylaxis be considered for children older than 15 years old and in younger postpubertal children with Injury Severity Score (ISS) greater than 25. For prepubertal children, even with ISS greater than 25, we conditionally recommend against routine pharmacologic prophylaxis. Second, in children hospitalized after trauma, we conditionally recommend mechanical prophylaxis be considered for children older than 15 years and in younger postpubertal children with ISS greater than 25 versus no prophylaxis or in addition to pharmacologic prophylaxis. Lastly, in children hospitalized after trauma, we conditionally recommend against active surveillance for VTE with ultrasound compared with routine daily physical examination alone for earlier detection of VTE. The limited pediatric data and paucity of high-quality evidence preclude providing more definitive recommendations and highlight the need for clinical trials of prophylaxis. (*J Trauma Acute Care Surg.* 2017;82: 627–636. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review/meta-analysis, level III.

KEY WORDS: Deep vein thrombosis; injury severity score; intensive care; pediatric; wounds and injuries.

In the past decade, the incidence of venous thromboembolism (VTE) in hospitalized children increased by nearly 70%, likely because of advancements in the care of critically ill children, increased awareness, and better detection methods.[1] In the short term, VTE in children is associated with prolonged hospitalization, pulmonary embolism, paradoxical embolic stroke, and even death, whereas in the long term, it is associated with prolonged anticoagulation, recurrence of VTE, and postthrombotic syndrome with limb swelling and pain due to venous insufficiency.[2] Venous thromboembolism is also associated with excess inpatient costs ranging from $12,000 to $28,000 per hospitalization.[3,4] Although the incidence of VTE in children is low, children hospitalized after trauma, similar to adults, are at increased risk of VTE.[1,5,6] Of the nearly one quarter of a million children hospitalized after trauma annually in the United States, 0.1% to 0.8% develop VTE.[3,7] Given the rising incidence of VTE in children and the resultant morbidity and excess cost, there is growing impetus for hospitals to institute local pediatric guidelines on VTE prophylaxis, particularly in high-risk populations, such as those hospitalized after trauma.

Unlike in adults, there is paucity of evidence on the risks and benefits of VTE prophylaxis in children.[2,5] As local pediatric guidelines on VTE prophylaxis are developed, it is imperative to evaluate the current state of evidence to determine what recommendations can be made. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology provides guidance for rating evidence quality and

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This study was presented at the 29th annual meeting of the Eastern Association for the Surgery of Trauma, January 12–16, 2016, in San Antonio, Texas.
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grading strength of recommendations.[8,9] Applying the GRADE methodology, a writing group from the Pediatric Trauma Society and the Practice Management Guidelines Section of the Eastern Association for the Surgery of Trauma developed recommendations with the goal of providing an evidence-based framework for hospitals that are developing local guidelines on VTE prophylaxis for children hospitalized after trauma.

OBJECTIVES

The primary objective of this guideline was to evaluate whether pharmacologic or mechanical prophylaxis reduces the incidence of VTE in children hospitalized after trauma and whether active surveillance with ultrasound (versus daily physical examination alone) results in earlier detection of VTE in this population. Our PICO (population [P], intervention [I], comparator [C], and outcome [O]) questions were as follows:

PICO Question 1

In children hospitalized after trauma (P), should pharmacologic VTE prophylaxis be utilized (I), compared with no pharmacologic prophylaxis (C), to reduce the incidence of VTE (O)?

PICO Question 2

In children hospitalized after trauma (P), should mechanical VTE prophylaxis be utilized (I), compared with no prophylaxis or in addition to pharmacologic prophylaxis (C), to reduce the incidence of VTE (O)?

PICO Question 3

In children hospitalized after trauma (P), should active surveillance for VTE with ultrasound be performed (I), compared with daily physical examination alone (C), to detect VTE earlier (O)?

A secondary objective was to evaluate putative risk factors for VTE in children hospitalized after trauma. The findings for this question were incorporated in PICO Question 1.

INCLUSION CRITERIA FOR THIS REVIEW

Study Types

We included case series, cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials. Original studies from meta-analyses and reviews were also included. Case reports, surveys, and letters to the editor were excluded.

Participant Type

Any patient 0 to 21 years old who developed VTE after being hospitalized for trauma was included. Similar children who did not develop VTE were included as control subjects.

Intervention Types

Pharmacologic VTE prophylaxis consisted primarily of low-molecular-weight heparin, particularly enoxaparin, unfractionated heparin, or warfarin. Mechanical prophylaxis consisted of pneumatic compression devices or compression stockings. Ultrasound scans of the lower extremities and of insertion sites for central venous catheters were used for active surveillance for VTE. The putative risk factors evaluated were age, severity of injury, presence of central venous catheters, major surgery, site and type of injury (i.e., acute spinal cord, pelvis fracture, femur fracture, head injury, abdominal injury, and chest injury), obesity, mechanical ventilation, use of recombinant factor VIIa, and immobilization.

Outcome Measure Type

The relevant outcomes were the incidence of VTE for PICO Questions 1 and 2 and time to detection of VTE for PICO Question 3. Via consensus, the writing group considered incidence of VTE as a critical outcome and time to detection of VTE an important outcome. Venous thromboembolism was defined as deep vein thrombosis in the extremities and/or pulmonary embolism. For PICO Questions 1 and 2, only symptomatic VTE was included because this was the most consistently reported outcome in pediatric studies. For PICO Question 3, VTE detected by active surveillance with ultrasound, regardless of symptoms, was compared with symptomatic VTE. We also used symptomatic VTE as outcome for the review of putative risk factors. Given the paucity of data, other relevant outcomes (e.g., duration of hospitalization, incidence of stroke, mortality rate, duration of anticoagulation, recurrence of VTE, incidence of postthrombotic syndrome, and costs of care) were not evaluated, even though the writing group considered these as important outcomes.

REVIEW METHODS

Search Strategy

A medical librarian performed a systematic review of the MEDLINE database using PubMed from January 1946 to July 2015. The search strategies included "venous thromboembolism," "trauma," and "pediatric," with additional subject headings and text words per concept and with added specific terms for "prophylaxis" and "prevention." The search was restricted to humans, availability of full text article, and publication in English language. Only clinical studies in a pediatric trauma population, defined as 21 years or younger, or studies that combined adults and children but had delineated analyses for children were analyzed.

Study Selection/Data Extraction

Abstracts were reviewed for relevance to the PICO questions of interest by one of the authors (A.M.). Potentially relevant studies underwent full text review by the entire writing group to determine inclusion. Conflicts were resolved through group consensus. Once the included articles were determined, data on the study type, subject characteristics, presence of putative risk factors for VTE, type of prophylaxis, presence of VTE, and strength of association between exposure, that is, prophylaxis or putative risk factor, and VTE were extracted into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington). Data were checked in duplicate for accuracy by two members of the writing group assigned to the PICO question. Inconsistencies were resolved through full group review of the data and discussion.

Assessment of Methodological Quality/GRADE Process

The quality of evidence for each PICO question was assessed by two members of the writing group. Based on the GRADE guidelines, randomized controlled trials and observational

studies were initially categorized as having high and low quality, respectively.[8] The category was upgraded or downgraded based on the five core GRADE domains of risk for bias, inconsistency, indirectness, imprecision, and publication bias, as well as the size of effect. The quality of evidence for each study was finalized after discussions with the entire writing group. We utilized GRADEpro (McMaster University and Evidence Prime Incorporated, Hamilton, Ontario, Canada), an online software, to create summary-of-findings tables for each PICO question.[10]

Measures of Treatment Effect

Because of the small number of studies available for each PICO question and significant differences in study design, meta-analysis was not performed, and summary measures of treatment effect were not calculated. Incidence of VTE was presented as counts (%), whereas that for time to detection of VTE was presented as median days. Comparisons for incidence of VTE were performed using Fisher exact test. For the putative risk factors, significant heterogeneity of studies or lack of control subjects prevented calculation of summary measures of effect. Strengths of association were expressed as odds or risk ratios.

RESULTS

The literature search yielded 48 articles (Fig. 1). A total of 34 articles (71%) were excluded mainly because of study design. There were no randomized controlled trials. Of the included studies, only two addressed, at most partially, the PICO questions of interest.[11,12] A total of 14 studies addressed the putative risk factors for VTE.[3,6,7,12–22] The age ranges for these studies were 0 to 15 years old (one study), 0 to16 years old (one study), 0 to 17 years old (four studies), 0 to 18 years old (one study), 0 to 19 years old (one study), 0 to 20 years old (two studies), and 0 to 21 years old (four studies).

Pharmacologic Prophylaxis in Children Hospitalized After Trauma (PICO Question 1)

In children hospitalized after trauma (P), should pharmacologic VTE prophylaxis be utilized (I), compared with no pharmacologic prophylaxis (C), to reduce the incidence of VTE (O)?

Qualitative Synthesis

The literature search yielded only one study with data on the incidence of VTE in children hospitalized after trauma who received pharmacologic prophylaxis compared with those who did not receive prophylaxis (Table 1). In this study, Hanson et al.[11] compared the incidence of VTE in children admitted to the intensive care unit after trauma during three time periods: prior to implementation of an institutional guideline for VTE prophylaxis using enoxaparin, rollout phase, and post–guideline implementation. The age ranges (median) of children in the three time periods were 0 to 18 (12) years old, 0 to 19 (10) years old, and 0 to 18 (7) years old, respectively. For purposes of this practice management guideline, only the preguideline and postguideline cohorts were included. In children at low risk of bleeding who received enoxaparin, 0 of 35 (0%) had symptomatic VTE compared with 9 of 308 children (2.9%) who did not receive enoxaparin ($p = 0.75$). This equated to 15 fewer (95% confidence interval [CI], 58 fewer to 28 more) VTE events per 1,000 critically ill children admitted after trauma. Low risk of bleeding in this study was defined as absence of intracranial bleeding, solid organ injury, planned surgical intervention or invasive procedure, and renal failure.

In the absence of evidence to support a recommendation for routine pharmacologic prophylaxis, we attempted to identify children hospitalized after trauma who are at high risk of VTE (Tables 2–4). Connelly et al.[6] published the first clinical prediction tool to predict VTE in children 0 to 17 years old who were hospitalized after trauma. The tool included Glasgow Coma Scale score, age, gender, intubation, admission to the intensive care unit, transfusion of blood products, placement of central venous catheter, pelvic and lower-extremity fracture, and major surgery. In derivation and validation cohorts, the tool performed well, with areas under the receiver operating characteristic curve greater than 0.90. A similar clinical prediction tool with similar findings was published while this guideline was under review.[23] The writing group was not able to critically appraise this publication or incorporate its findings into this guideline.

Adult trauma victims are known to be at risk of VTE, leading to concern that the risk of VTE in children hospitalized after

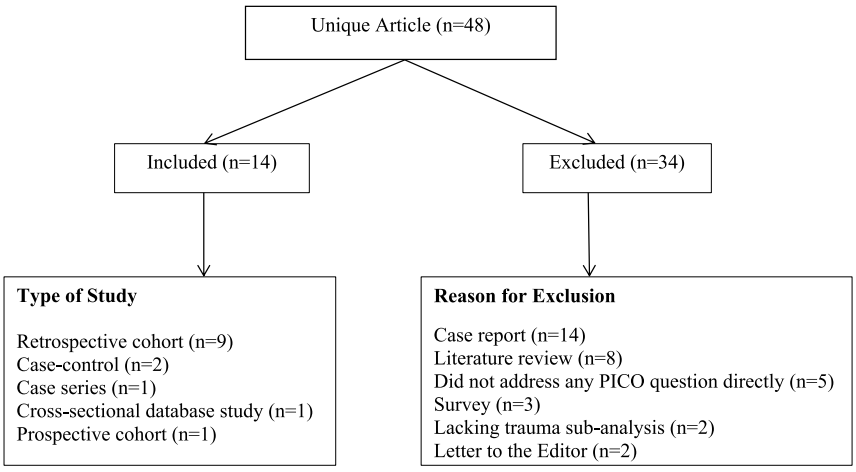

Figure 1. Flow diagram of included studies. Studies were excluded primarily based on the study design.

TABLE 1. Summary of Findings for Prophylaxis Against VTE

Quality Assessment							No. of Patients		Effect			
No. of Studies	Study Design	Risk for Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
PICO Question 1: In children hospitalized after trauma (P), should pharmacologic VTE prophylaxis be utilized (I), compared with no pharmacologic prophylaxis (C), to reduce the incidence of VTE (O)?												
Outcome: Incidence of extremity deep vein thrombosis and/or pulmonary embolism assessed radiologically												
1	Observational studies	Serious	Not serious	Not serious	Very serious		Pharmacologic prophylaxis: 0/35 (0.0%)	No prophylaxis: 9/308 (2.9%)	Not estimable	15 Fewer per 1,000 (from 58 fewer to 28 more)	⊕○○○ Very low	Critical
PICO Question 2a: In children hospitalized after trauma (P), should mechanical VTE prophylaxis be utilized (I), compared with no prophylaxis (C), to reduce the incidence of VTE (O)?												
Outcome: Incidence of extremity deep vein thrombosis and/or pulmonary embolism assessed radiologically												
2	Observational studies	Very serious	Very serious	Very serious	Very serious		Mechanical prophylaxis: 2/1,074 (0.2%)	No prophylaxis: 215/34,451 (0.6%)	Risk ratio: 0.30 (0.07 to 1.20)	4 Fewer per 1,000 (from 1 to 7 fewer)	⊕○○○ Very low	Critical
PICO Question 2b: In children hospitalized after trauma (P), should mechanical VTE prophylaxis be utilized (I), in addition to pharmacologic prophylaxis (C), to reduce the incidence of VTE (O)?												
Outcome: Incidence of extremity deep vein thrombosis and/or pulmonary embolism assessed radiologically												
1	Observational studies	Serious	Not serious	Very serious	Not serious		Mechanical prophylaxis: 0/49 (0%)	Additional pharmacologic prophylaxis: 0/11 (0.0%)	Not estimable	Not estimable	⊕○○○ Very low	Critical
PICO Question 3: In children hospitalized after trauma (P), should active surveillance for VTE with ultrasound be performed (I), compared with daily physical examination alone (C), to detect VTE earlier (O)?												
Outcome: Time to detection of venous thromboembolic event in days												
1	Observational studies	Very serious	Not serious	Not serious	Not serious		Active surveillance with ultrasound: 169	Physical exam alone: 307	—	Median 3 d fewer	⊕○○○ Very low	Important

TABLE 2. Association of Age and VTE in Children Hospitalized After Trauma

Reference	Population	Age Group*	VTE Incidence**	Risk for VTE (95% CI)
Vavilala et al[22]	All trauma	<5	0.2	Reference group
		5–9	0.4	aRR, 2.0 (0.5–7.8)
		10–15	1.3	aRR, 5.0 (1.5–16.7)
Van Arendonk et al[7]	All trauma	<12	1	Reference group
		13–15	3	aOR, 2.0 (1.5–2.5)
		16–21	8	aOR, 3.8 (3.0–4.8)
Connelly et al[6]	All trauma	0	0.7	Reference group
		1–9	1.8	aOR, 0.4 (0.3–0.6)
		10–12	1.1	aOR, 0.9 (0.5–1.4)
		13–15	2.6	aOR, 1.3 (0.9–1.9)
		16–17	5.5	aOR, 1.7 (1.2–2.4)
O'Brien and Candrilli[19]	All trauma; >1 d in intensive care unit	<1	3.8	OR, 1.8 (1.4–2.3)
		1–4	1.8	Reference group
		5–9	1.8	OR, 1.0 (0.8–1.3)
		10–13	2.5	OR, 1.1 (0.9–1.4)
		14–17	6.2	OR, 2.3 (2.0–2.8)
		18–21	9.9	OR, 3.0 (2.5–3.6)
Harris and Lam[17]	Traumatic brain injury	<1	2.5	Reference group
		1–9	1.2	aOR, 0.8 (0.4–1.9)
		10–14	2.3	aOR, 1.5 (0.6–3.5)
		15–20	7.6	aOR, 3.7 (1.8–8.0)
Jones et al[18]	Spinal cord injury	<14	11	aOR, 0.2 (0.1–0.7)
		14–19	44	aOR, 0.7 (0.5–1.0)
		30–49	67	Reference group

*In years.
**Per 1,000 children.
aOR indicates adjusted odds ratio; ARR, adjusted risk ratio.

trauma is higher after the onset of puberty.[24] Of four studies that analyzed children 0 years to 15 to 21 years old who were hospitalized after trauma, children older than 10 to 15 years (depending on the reference group) had increased risk of VTE (Table 2).[6,7,19,22] In a cohort of children 0 to 17 years old, Connelly et al.[6] demonstrated increased risk of VTE in children older than 15 years, but not for those 10 to 15 years old. In two additional database analyses of children with specific injuries, children 15 to 20 years old with traumatic brain injury had higher incidence of VTE compared with children 0 to 14 years old, whereas those 0 to 14 years old with acute spinal cord injury had lower incidence of VTE than did the reference adult group (30–49 years old).[17,18] In a recent national Delphi consensus study among pediatric trauma experts, consensus was reached that VTE prophylaxis should not be given to children 12 years or younger except in exceptional cases.[24]

Different thresholds of Injury Severity Score (ISS) have been used to define children at increased risk of VTE (Table 3). Among unselected children hospitalized after trauma, an ISS 25 or greater was strongly associated with VTE.[3,7,22] In subsets of children admitted to the intensive care unit or those with prolonged hospitalization, a score greater than 9 conferred higher risk of VTE.[15,19] The interaction between ISS and age of the child was not addressed in these studies. In the national Delphi consensus study, near-consensus was reached in favor of VTE prophylaxis in children with multiple major trauma or an ISS score greater than 25.[24]

The associations between the other putative risk factors, that is, central venous catheter, major surgery, site and type of injury (i.e., acute spinal cord, pelvis fracture, femur fracture, head injury, abdominal injury, and chest injury), obesity, mechanical ventilation, and immobilization, and VTE in children hospitalized after trauma, remain unclear (Table 4).[3,6,7,12,13,15–17,19,20,22] The odds ratios ranged from 0.8 to 64.0, depending on the putative risk factor. No studies provided the strength of association between the use of recombinant factor VIIa and VTE.

Grading the Evidence

With the use of the GRADE framework for evaluating the data specifically related to the outcome of incidence of VTE, very serious concerns about imprecision in the estimates were found (Table 1). Therefore, the overall quality of this evidence was downgraded from low to very low.

DISCUSSION

An analysis of available evidence showed an absence of high-quality studies comparing the incidence of VTE in children hospitalized after trauma with respect to exposure to

TABLE 3. Association of ISS and VTE in Children Hospitalized After Trauma

Reference	Population	Score	VTE Incidence*	Risk for VTE (95% CI)
Candrilli[3]	All trauma	<9	0.9	Reference group
		9–15	4	aOR, 2.1 (1.5–3.1)
		16–25	5	aOR, 2.5 (1.6–3.7)
		>25	16	aOR, 3.5 (2.0–6.2)
Vavilala et al[22]	All trauma	<9	0.2	Reference group
		9–15	1.5	aRR, 5.8 (2.4–13.6)
		16–24	2.2	aRR, 7.4 (2.5–21.4)
		≥25	8.1	aRR, 21.4 (8.4–54.3)
Van Arendonk et al[7]	All trauma	<9	0.4	Reference group
		9–15	3	aOR, 4.0 (3.1–5.1)
		16–24	6	aOR, 5.9 (4.6–7.8)
		25–75	26	aOR, 7.2 (5.4–9.6)
Connelly et al[6]	All trauma	<9	0.3	Not reported
		9–15	1.4	Not reported
		16–24	5.3	Not reported
		25–75	19	Not reported
Cyr[15]	Severe injury admitted to intensive care unit or length of stay >72 h	<9	Not reported	Reference group
		≥9	Not reported	OR, 5.3 (1.6–17.3)
O'Brien and Candrilli[19]	Trauma >1 d in intensive care unit	<9	0.9	Not reported
		9–15	2.9	Not reported
		16–24	5.8	Not reported
		≥25	14	Not reported

*Per 1,000 children.
aOR indicates adjusted odds ratio; ARR, adjusted risk ratio.

TABLE 4. Association of Other Putative Risk Factors and VTE in Children Hospitalized After Trauma

Putative Risk Factor	No. of Studies (With Odds Ratios)	Range of Odds Ratios	GRADE Quality Level
Central venous catheter[7,13,15–17,19,20,22]	8 (7)	1.3–64.0	C
Major surgery*[7,19,20,22]	4 (3)	0.8–5.0	C
Acute spinal cord injury[7,15,16,19,20,22]	6 (3)	1.8–37.4	C
Pelvis fracture[7,13,19,20,22]	5 (2)	1.2–1.6	C
Femur fracture[7,13,16,19,20,22]	6 (3)	1.0–3.3	C
Head injury[7,19,20,22]	4 (2)	1.3–4.8	C
Abdominal injury[7,15,22]	3 (1)	7.7	C
Chest injury[7,15,22]	3 (2)	2.7–6.9	C
Obesity[7]	1 (1)	3.0	C
Mechanical ventilation[7,17,19,20]	4 (3)	0.9–2.5	C
Recombinant factor VIIa[16]	1 (0)	—	D
Immobilization**[16]	1 (1)	0.8–10	C

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Methodology Levels for Rating the Quality of Evidence:[8] A/high: very confident that the true effect lies close to estimate of effect; B/moderate: moderate effect; true effect is likely close to estimate of effect but may be substantially different; C/low: limited confidence; true effect may be substantially different from estimate of effect; D/very low: little confidence; true effect likely substantially different from estimate of effect.

*In two studies, major surgery included craniotomy, spinal procedure, open reduction/internal fixation, and laparotomy.[19,22]

**Immobilization was defined to include neuromuscular blockade >24 hours, deep sedation >24 hours, and Glasgow coma Scale score <8 on admission.

pharmacologic prophylaxis. The described work by Hanson et al.[11] showed a nonsignificant decrease in VTE with the use of enoxaparin in children at low risk of bleeding. The writing group excluded asymptomatic VTE identified by guideline-directed screening ultrasound in the analysis. It is possible that some of these VTE would eventually have become symptomatic. In adults with major trauma who are at low risk of bleeding, pharmacologic prophylaxis is recommended because of its proven efficacy and safety.[5] In addition, available evidence suggests that pharmacologic prophylaxis in children is relatively safe with regard to bleeding events, both after trauma and in other clinical settings.[25–27]

The available literature suggests that increasing age, particularly older than 15 years, and severe injury, defined as an ISS greater than 25, are associated with increased risk of VTE. In an attempt to combine the risks of VTE due to multiple factors, clinical prediction tools have been developed.[6,23] While these tools may improve our ability to identify the small cohort of children hospitalized after trauma who are at high risk of VTE, they do not provide any information on the efficacy and safety of pharmacologic prophylaxis.[28] Because of this significant gap in knowledge, the writing group unanimously decided to focus the recommendation only to children older than 15 years or those with an ISS greater than 25. Because of the maturation of the coagulation system during puberty, it is likely that the risk of VTE in younger postpubertal children approaches that of older children in the presence of an ISS greater than 25.[29,30] Similar extrapolations are not necessarily appropriate for prepubertal children with ISS greater than 25 but should be investigated. Onset of puberty, as defined by Tanner Stage 2 genital and pubic hair growth, has been shown to occur as early as 9 years in boys and 9.5 years in girls, depending on ethnicity.[31] The writing group agreed that it is possible that younger children or those with less severe injuries do not need pharmacologic prophylaxis, whereas children with multiple risk factors may need prophylaxis. However, with limited data on the efficacy and safety of pharmacologic prophylaxis in children, the writing group was unable to make any recommendations for these cohorts of children. Until such evidence becomes available, the writing group recommends that this guideline should be meant to provide a basic framework for the judicious use of pharmacologic prophylaxis in children hospitalized after trauma who are at highest risk of VTE. Similarly, based on current clinical practice, we suggest the use of enoxaparin over unfractionated heparin for pharmacologic prophylaxis.

Recommendation for Pharmacologic Prophylaxis in Children Hospitalized After Trauma (PICO Question 1)

We conditionally recommend that pharmacologic prophylaxis be considered for children older than 15 years who are at low risk of bleeding. We also conditionally recommend that pharmacologic prophylaxis be considered for children younger than 15 years old who are postpubertal if they have an ISS greater than 25. For prepubertal children, even with ISS greater than 25, we conditionally recommend against routine pharmacologic prophylaxis. Further studies are necessary to provide recommendations in prepubertal children. These recommendations are conditional, given the paucity of published data in children and the very low quality of the available evidence. Our recommendations are based on data in adults and the relative safety of enoxaparin at prophylactic doses in children.[5,25–27]

Mechanical VTE Prophylaxis in Children Hospitalized After Trauma (PICO Question 2)

In children hospitalized after trauma, should mechanical VTE prophylaxis be utilized, compared with no prophylaxis or in addition to pharmacologic prophylaxis, to reduce the incidence of VTE?

Qualitative Synthesis

The literature search yielded only two observational studies providing data on the incidence of VTE in children hospitalized after trauma who received mechanical prophylaxis compared with those who did not receive prophylaxis (Table 1). In the first study, Azu et al.[12] retrospectively compared the incidence of VTE in children admitted to a Level I trauma center for three age groups: Group I (0–12 years old), Group II (13–17 years old), and Group III (>17 years old). By local clinical practice, all children of adult size received mechanical prophylaxis, although its use was not documented. Children in Group I did not routinely receive any form of prophylaxis. Group II had pharmacologic prophylaxis ordered at the discretion of the attending surgeon. Its use was also not documented. Of the 1,025 children in Group II, two symptomatic VTE events occurred despite the presumed use of pneumatic compression device.

In the second observational study by Hanson et al.,[11] children at high risk of VTE and bleeding were recommended to receive pneumatic compression device per guideline. There were 60 children 0 to 18 years old in this category in the post-guideline period, of whom 49 received the device only and 11 received pharmacologic prophylaxis after the bleeding risk diminished. A total of three VTE events, none of which were symptomatic, were identified in children who received the device only. The use of the device was not documented but was inferred from the guideline.

Neither study by Azu et al.[12] nor that of Hanson et al.[11] provided a comparable group of children who were not on any prophylaxis. To estimate the proportion of these children who developed VTE, we used data from the National Trauma Data Bank (NTDB) between 2000 and 2005 as reported by O'Brien and Candrilli.[19] Although NTDB does not record the use of pharmacologic or mechanical prophylaxis, the use of these interventions is uncommon in children.[13,32] The data from the 14- to 17-year age group was used to compare with the similarly aged Group II in the study by Azu et al.,[12] in which mechanical prophylaxis was used.

Based on these studies, 2 (0.2%) of 1,074 children who received mechanical prophylaxis had symptomatic VTE, whereas 215 (0.6%) of 34,451 children who did not receive mechanical prophylaxis (from the NTDB) had VTE ($p = 0.08$) (Table 1). This equated to 4 fewer (95% CI, 1–7 fewer) VTE events per 1,000 children hospitalized after trauma with mechanical prophylaxis versus no prophylaxis. In children who received pharmacologic prophylaxis in addition to mechanical prophylaxis, none of 11 children had symptomatic VTE, which was similar to none of 49 children solely on mechanical prophylaxis who had symptomatic VTE.

Grading the Evidence

With the use of the GRADE framework for evaluating the data specifically related to the outcome of incidence of VTE, very serious concerns about risk for bias, inconsistency, indirectness, imprecision in the estimates, and lack of control for potential confounders were found (Table 1). Therefore, the overall quality of this evidence was downgraded from low to very low.

DISCUSSION

Analysis of available evidence showed an absence of high-quality studies comparing the incidence of VTE in children hospitalized after trauma with respect to exposure to mechanical prophylaxis. Inferred from the studies by Azu et al.[12] and Hanson et al.,[11] the use of mechanical, versus no prophylaxis, suggested a possible reduction on the incidence of VTE.[11,12] This effect is strengthened by data in adults showing significant reduction in the incidence of VTE after trauma with mechanical prophylaxis.[33] The writing group also gave weight to tolerability and safety of mechanical VTE prophylaxis. Mechanical prophylaxis was well accepted by pediatric providers in a multinational study with 24% of children 8 to 18 years old who were admitted to the intensive care unit receiving mechanical prophylaxis.[32]

Based on limited pediatric evidence, children on mechanical prophylaxis had similar risk of VTE compared with those on pharmacologic prophylaxis in addition to mechanical prophylaxis.[11] In adults who were hospitalized after trauma, pharmacologic prophylaxis was superior to mechanical prophylaxis in reducing the incidence of VTE.[5] Based on the potential benefits and relative safety of mechanical prophylaxis in children, it is reasonable to use mechanical prophylaxis alone or in addition to pharmacologic prophylaxis in children hospitalized after trauma at high risk of VTE. A potential limitation is the availability of appropriately sized sleeves for younger children.

Recommendation for Mechanical Prophylaxis in Children Hospitalized After Trauma (PICO Question 2)

We conditionally recommend that mechanical prophylaxis be considered alone or in addition to pharmacologic prophylaxis to hospitalized children older than 15 years and children younger than 15 years who are postpubertal if they have an ISS greater than 25 for whom an appropriately sized device is available. This recommendation is conditional, given the paucity of published data in children and the very low quality of the available evidence. Our recommendation is based on data in adults and the safety and tolerability of mechanical prophylaxis in children.[5,32]

Active Ultrasound Surveillance for VTE in Children Hospitalized After Trauma (PICO Question 3)

In children hospitalized after trauma, should active surveillance for VTE with ultrasound be performed, compared with daily physical examination alone, to detect VTE earlier?

Qualitative Synthesis

A single prospective study by Hanson et al.[11] incorporated screening ultrasound as part of a larger clinical care guideline in children 0 to 18 years old at high risk of VTE after admission to the intensive care unit after trauma (Table 1). Active surveillance with ultrasound was utilized in children at high risk of VTE and also at high risk of bleeding that would prevent safe use of pharmacologic prophylaxis. Children received ultrasound of both lower extremities and the upper extremity in which a central venous catheter was inserted on hospital Day 7 if they were still in the intensive care unit. Of 60 eligible children, 26% received ultrasound. Compared with unselected historical control subjects who did not have active surveillance with ultrasound, the guideline care group had asymptomatic VTE detected 3 days earlier. The published results did not allow for comparison of the high-risk group of children who received active surveillance to a comparable high-risk control group.

Grading the Evidence

With the use of the GRADE framework for evaluating the data specifically related to the outcome of time to detection of VTE, very serious concerns about risk for bias and lack of control for potential confounders were found (Table 1). Therefore, the overall quality of this evidence was downgraded from low to very low.

Discussion

The value of active surveillance for VTE with ultrasound in children hospitalized after trauma is unclear. The single prospective study that incorporated active surveillance with ultrasound as part of a larger care guideline showed an earlier diagnosis of VTE, although all of these events were asymptomatic.[11] While it seems intuitive that active surveillance with ultrasound would detect VTE before it becomes symptomatic, the timing, frequency, and extent required of such a strategy is unclear. Furthermore, the natural history of asymptomatic VTE in children is poorly described. Earlier diagnosis of VTE with active ultrasound surveillance may lead to increased use of therapeutic anticoagulation without clear benefit. In adults, active surveillance for DVT with ultrasounds was not efficacious in reducing the risk of symptomatic VTE.[34] It may, in fact, increase the risk of bleeding with therapeutic anticoagulation for any detected asymptomatic DVT. The risk of major bleeding with therapeutic anticoagulation in children can be as high as 24% with unfractionated heparin and 4% with enoxaparin.[2,35] In addition, the cost of widespread active surveillance with ultrasound for these uncommon events would need to be considered before general utilization could be recommended.

Recommendation for Active Ultrasound Surveillance for VTE in Children Hospitalized After Trauma (PICO Question 3)

We conditionally recommend against active surveillance for VTE with ultrasound for earlier detection of VTE compared with routine daily physical examination alone in children hospitalized after trauma. The potential benefits of earlier detection and treatment of VTE are unclear, but the risk of bleeding with therapeutic anticoagulation is well documented.

FURTHER INVESTIGATION

The detailed review of the literature performed for this practice management guideline highlighted the paucity of data on VTE in children hospitalized after trauma. The evidence for pharmacologic and mechanical VTE prophylaxis in children is very low compared with adults.[36] Despite the developmental differences in the hemostatic system between children and adults that may affect the incidence of VTE and response to therapy, the writing group had to consider adult evidence in making the recommendations.[2] There is minimal evidence regarding effective risk stratification in children hospitalized after trauma. An initial approach for identifying children suitable for prophylaxis would be to focus on children older than 15 years. Clinical prediction tools should be easy to calculate at the bedside and should avoid risk markers such as ISS that are impracticable and lack acute pragmatic value. Risk stratification studies and subsequent randomized controlled trials are urgently needed to define the efficacy and safety of prophylaxis against VTE in children hospitalized after trauma. Because the numbers of critically injured patients and VTE are lower in children than in adults, traditional study designs based on the frequentist approach may not be feasible. The Bayesian approach, in which data from adults are formally incorporated in the design and adaptive randomization is used, may result in a smaller sample size and increase the likelihood of successfully completing the trial.[28]

The incidence of VTE was the only outcome evaluated in this guideline. The effect of VTE prophylaxis on other outcomes, such as duration of hospitalization, incidence of stroke, mortality rate, duration of anticoagulation, recurrence of VTE, incidence of postthrombotic syndrome, and costs of care, should be studied. The risks, sites, and severity of bleeding with VTE prophylaxis should also be explored.

USING THESE GUIDELINES IN CLINICAL PRACTICE

These guidelines represent a detailed summary of the limited literature regarding VTE prophylaxis in children hospitalized after trauma. The available evidence is of very low quality and observational in nature. As such, evidence from adults was considered in the writing group's recommendations. These guidelines are intended to inform the decision-making process rather than replace clinical judgment.

CONCLUSIONS

In summary, we have provided evidence-based recommendations using the GRADE methodology (Table 5). First, in children hospitalized after trauma who are at low risk of bleeding, we conditionally recommend the use of pharmacologic prophylaxis be considered in children older than 15 years and in younger postpubertal children with ISS greater than 25. We conditionally recommend against the use of routine pharmacologic prophylaxis in prepubertal children, even with ISS greater than 25. Second, in children hospitalized after trauma, we conditionally recommend mechanical prophylaxis versus no prophylaxis or in addition to pharmacologic prophylaxis be considered in children older than 15 years and in younger postpubertal children with ISS greater than 25. Lastly, in children hospitalized after trauma, we conditionally recommend against active surveillance for VTE with ultrasound compared with routine daily physical examination alone for earlier detection of VTE.

TABLE 5. Summary of Recommendations

Question	Recommendation
PICO Question 1	In children hospitalized after trauma who are at low risk of bleeding, we conditionally recommend pharmacologic prophylaxis be considered for those >15 y old and in younger postpubertal children with ISS >25. We conditionally recommend against the use of routine pharmacologic prophylaxis in prepubertal children, even with ISS >25.
PICO Question 2	In children hospitalized after trauma, we conditionally recommend mechanical prophylaxis be considered for those >15 y old and in younger postpubertal children with ISS >25 versus no prophylaxis or in addition to pharmacologic prophylaxis.
PICO Question 3	In children hospitalized after trauma, we conditionally recommend against active surveillance for VTE with ultrasound compared with daily physical examination alone for earlier detection of VTE.

AUTHORSHIP

A.M. conducted initial review of potential articles. Data collection from selected articles was divided among the entire author group. Data analysis and interpretation were done by the entire author group. A.M. and E.V.S.F. wrote the initial draft of the manuscript, and all authors contributed to revisions.

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DISCLOSURE

S.J.H. is a site investigator for an anticoagulation trial sponsored by Bristol-Myers Squibb. S.H.O. is the principal investigator and a steering committee member for anticoagulation trials sponsored by Bristol-Myers Squibb and Pfizer. S.H.O. is also a member of the data and safety monitoring board for GlaxoSmithKline. E.V.S.F. is a member of the data and safety monitoring board for an anticoagulation trial sponsored by GlaxoSmithKline and is partially supported by a grant from the American Heart Association.

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