Date: February 18, 2014

Title: Venous Thromboembolism (VTE) Prophylaxis in Children and Adolescents

Clinical Question

P	*(Population/Problem)*	Among hospitalized children
I	*(Intervention)*	does risk assessment and stratified venous thromboembolism* prophylaxis
C	*(Comparison)*	compared to no prophylaxis
O	*(Outcome)*	reduce VTE occurrence without an increase in significant adverse effects?

***Definitions** for terms marked with * may be found in the Supporting Information section.*

Target Population for the Recommendation

Include: Hospitalized patients age 10 to 17 years (up to the 18th birthday)
Exclude: Patients:

- 18 years and older
  (eligible for assessment and treatment by adult guidelines *(Falck-Ytter 2012 [5a], Gould 2012 [5a], Kahn 2012 [5a])*)
- with current venous thromboembolism

Recommendations

1. It is recommended that patients age 10 to 17 years who are expected to have a surgical procedure lasting at least 60 minutes be started at induction of anesthesia on a sequential compression device* (SCD), for prophylaxis of venous thromboembolism (VTE), unless there are contraindications to mechanical prophylaxis* *(Schwenk 1998 [2b], Local Consensus 2014 [5], Coleridge-Smith 1990 [5], Branchford 2012 [5b])*. See Table 1.

Table 1: Contraindications to mechanical prophylaxis

- DVT, suspected or existing (can use graduated compression stockings)
- 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

(Local Consensus 2014 [5], Branchford 2012 [5b])

Abbreviations for recommendations, tables and text: BMI = body mass index; CCHMC = Cincinnati Children's Hospital Medical Center; CI = confidence interval; CVC = central venous catheter; DVT = deep vein thrombosis; IBD = inflammatory bowel disease; ICU = intensive care unit; LMWH = low molecular weight heparin; mm^3 = cubic millimeter; mOsm/kg = milliOsmoles per kilogram; PICC = peripherally-inserted central catheter; PIV = peripheral intravenous; RR = relative risk; SCD = sequential compression device; SLE = systemic lupus erythematosus; TPN = total parenteral nutrition; VTE = venous thromboembolism

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

   (Branchford 2012 [4a], Sharathkumar 2012 [4a], Local Consensus 2014 [5]). See Algorithm.

Table 2: VTE risk factors

VTE risk factor	Studies
• blood stream infection	*(Branchford 2012 [4a], Sharathkumar 2012 [4a], Wright 2011 [4a])*
• central venous catheter (including non-tunneled, tunneled and PICCs)	*(O'Brien 2011 [3a (incidence); 4a (risk factors)], Vavilala 2002 [3a (incidence); 4a (risk factors)], Cyr 2006 [3b (incidence); 4b (risk factors)], Takemoto 2013 [4a], Askegard-Giesmann 2012 [4a], Branchford 2012 [4a], Sharathkumar 2012 [4a], Wright 2011 [4a], Hanson 2012 [4b], Grandas 2000 [4b])*
• history of venous thrombosis	*(Hanson 2012 [4b])*
• hyperosmolar state (serum osmolality >320 mOsm/kg)	*(Local Consensus 2014 [5])*
• inflammatory diseases (e.g. IBD, SLE)	*(Takemoto 2013 [4a], Branchford 2012 [4a], Vu 2008 [4a], Hanson 2012 [4b])*
• medications: asparaginase	*(Local Consensus 2014 [5], Monagle 2012 [5a])*
• medications: estrogen use (within past two months)	*(Sharathkumar 2012 [4a], Hanson 2012 [4b])*
• obesity (BMI > 95th percentile for age)	*(Sharathkumar 2012 [4a], Rana 2009 [4a], Vu 2008 [4a], Local Consensus 2014 [5])*
• oncologic diagnosis	*(Takemoto 2013 [4a], Wright 2011 [4a], Hanson 2012 [4b], Local Consensus 2014 [5], Monagle 2012 [5a])*
• orthopedic procedures: hip or knee reconstruction	*(Local Consensus 2014 [5], Falck-Ytter 2012 [5a])*
• nephrotic syndrome	*(Takemoto 2013 [4a], Wright 2011 [4a], Local Consensus 2014 [5], Monagle 2012 [5a])*
• thrombophilia – known, or family history of clots	*(Wright 2011 [4a], Hanson 2012 [4b])*
• trauma: > 1 lower extremity long bone fracture, complex pelvic fractures, spinal cord injury	*(O'Brien 2011 [3a (incidence); 4a (risk factors)], Candrilli 2009 [3a (incidence); 4a (risk factors)], Vavilala 2002 [3a (incidence); 4a (risk factors)], Cyr 2006 [3b (incidence); 4b (risk factors)], Askegard-Giesmann 2012 [4a], Hanson 2012 [4b])*

Table 3: Determining VTE risk category

Expected **altered mobility*** > 48 hours?	+ Number of **VTE risk factors**	= **Risk category**
No	None	Low
No	1 or more	Moderate
Yes	0 or 1	Moderate
Yes	2 or more	High

(Branchford 2012 [4a], Sharathkumar 2012 [4a], Hanson 2012 [4b], Local Consensus 2014 [5], Branchford 2012 [5b])

3. It is recommended that VTE prophylaxis be administered based on risk category (see Table 4), as soon as feasible but within 24 hours of assessment, unless there are contraindications (see Table 1 and Table 5). See Algorithm.

   Note: Examples of risk factor mitigation strategies are: discontinuing PICC lines as soon as possible, treating infections, and avoiding estrogen therapy.

Table 4: VTE prophylaxis stratified by risk category

Low risk	Moderate risk	High risk
a. encourage early ambulation	a. encourage early ambulation	a. encourage early ambulation
b. mitigate risk factors (see note)	b. mitigate risk factors (see note)	b. mitigate risk factors (see note)
	c. administer mechanical prophylaxis see Table 1 • SCD preferred (and/or graduated compression stockings) • make efforts to achieve 18 hours of daily use	c. administer mechanical prophylaxis see Table 1 • SCD preferred (and/or graduated compression stockings) • make efforts to achieve 18 hours of daily use
		d. consider pharmacologic prophylaxis see Table 5 • obtain hematology consultation when weighing risk versus benefit in patients at risk of bleeding

(Alhazzani 2013 [1a], Barrera 2013 [1a], Ho 2013 [1a], Handoll 2002 [1a], Bidlingmaier 2011 [1b], Kakkos 2011 [1b], Arabi 2013 [3a], Stem 2013 [3b], Local Consensus 2014 [5], Branchford 2012 [5b])

Table 5: Contraindications to pharmacologic prophylaxis

Absolute contraindications	Relative contraindications
• bleeding disorder, known or tendency • hemorrhage, evidence of or high risk of • platelet count unable to be sustained > 50,000/mm^3	• intracranial mass • lumbar puncture or epidural catheter removal in prior 12 hours • neurosurgical procedure • pelvic fracture within past 48 hours • uncontrolled hypertension

(Local Consensus 2014 [5], Horlocker 2010 [5a], Branchford 2012 [5b])

4. It is recommended, if planning to initiate pharmacologic prophylaxis:
   a. in surgical patients seek surgical input regarding bleeding risk, prior to initiation
   b. see CCHMC Low Molecular Weight Heparin Dosing and Monitoring Guideline for management of LMWH prophylaxis
   c. obtain hematology consultation when considering alternative pharmacologic agents

(Alhazzani 2013 [1a], Barrera 2013 [1a], Handoll 2002 [1a], Bidlingmaier 2011 [1b], Kakkos 2011 [1b], Stem 2013 [3b], Local Consensus 2014 [5])

Discussion/Synthesis of Evidence related to the recommendations

The grade of the body of evidence to support risk assessment is moderate. Risk assessment is based on pediatric studies with weak study design, however the results among the many studies are consistent. The 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 – Prolonged Surgery

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 surgery *(Coleridge-Smith 1990 [5])*.

Risk Factors – Altered Mobility

Altered mobility serves as the main factor for risk stratification in the algorithm. 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 *(Sharathkumar 2012 [4a])*. A number of factors associated with VTE identified in pediatric retrospective studies are thought to confer risk due to their contribution to altered mobility; these include obesity, prolonged hospitalization, increasing severity of injury, mechanical ventilation and ICU admission *(O'Brien 2011 [3a (incidence); 4a (risk factors)], Candrilli 2009 [3a (incidence); 4a (risk factors)], Truitt 2005 [3a (incidence); 4a (risk factors)], Vavilala 2002 [3a (incidence); 4a (risk factors)], Cyr 2006 [3b (incidence); 4b (risk factors)], Askegard-Giesmann 2012 [4a], Branchford 2012 [4a], Sharathkumar 2012 [4a], Rana 2009 [4a], Azu 2005 [4b], Local Consensus 2014 [5])*

Risk Factors – Others

One prospective *(Hanson 2010 [2a (incidence); 3a (risk factors)])* and multiple retrospective studies, including two with a control comparison *(Branchford 2012 [4a], Sharathkumar 2012 [4a])* evaluating risk factors for VTE in pediatric trauma, surgery and medical patients showed consistency *(O'Brien 2011 [3a (incidence); 4a (risk factors)], Candrilli 2009 [3a (incidence); 4a (risk factors)], Truitt 2005 [3a (incidence); 4a (risk factors)], Vavilala 2002 [3a (incidence); 4a (risk factors)], Cyr 2006 [3b (incidence); 4b (risk factors)], Takemoto 2013 [4a], Askegard-Giesmann 2012 [4a], Greenwald 2012 [4a], Wright 2011 [4a], Vu 2008 [4a], Azu 2005 [4b], Grandas 2000 [4b])*. Key risk factors identified in these studies, in addition to those related to altered mobility, were TPN, CVC, estrogen use, positive blood stream infection, surgery, inflammatory disease, specific injuries (such as spinal cord, pelvic fracture and long bone fracture injuries), specific procedures (such as spinal procedures and an open reduction and internal fixation of a lower extremity long bone), increasing age and family history of thrombophilia. In one retrospective study, patients with nephrotic syndrome had a markedly increased rate of hospital-acquired VTE as did patients with oncologic diagnoses *(Takemoto 2013 [4a])*. Specifically, leukemia was the most frequent diagnosis associated with hospital-acquired VTE *(Takemoto 2013 [4a])*.

Other risk factors included in the algorithm by the working group were based on adult studies and local consensus: asparaginase therapy, hyperosmolar state and total hip or knee replacement *(Local Consensus 2014 [5], Falck-Ytter 2012 [5a], Monagle 2012 [5a])*.

Risk Factors – Combined effect

Some studies demonstrated the combination effect of multiple risk factors. For example, the combination of mechanical ventilation, systemic infection and hospitalization five days or more gave a post-test probability of VTE of 3.1% (compared to pre-test probability of 0.35%) *(Branchford 2012 [4a])*. Also, a prospective study noted an increase in odds of VTE development for each additional CVC placed (7.9-fold increase; p=0.005), for each additional risk factor present[1] (3-fold increase; p=0.009) and for increasing severity of injury (1.3-fold increase; p=0.03) *(Hanson 2010 [2a (incidence); 3a (risk factors)])*. And lastly, a retrospective study noted a 4-fold increase of hospital-associated VTE in patients with at least 4 complex chronic conditions compared to patients with only 1 chronic condition *(Takemoto 2013 [4a])*.

Timing of VTE Risk

In the Sharathkumar (2012) study, the majority of VTE events were diagnosed within a week of hospitalization (mean of 7 days and median of 3 days) *(Sharathkumar 2012 [4a])*. The median time to VTE diagnosis was also similar in Branchford (2012) at 7 days *(Branchford 2012 [4a])*. Therefore, we recommend reassessing risk of VTE at 48 to 72 hours.

[1] Statistically significant risk factors identified in this study were: TPN, CVC, deep sedation, neuromuscular blockade, inotropic support and factor VIIa administration *(Hanson 2010 [2a (incidence); 3a (risk factors)])*.

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 of VTE. The relative risk (RR) of DVT in patients treated with mechanical methods compared to no treatment ranges from RR=0.31 (95%CI 0.19, 0.51) in hip fracture patients *(Handoll 2002 [1a])* to RR=0.55 (95%CI 0.34, 0.99) in trauma patients *(Barrera 2013 [1a])*. Another large meta-analysis of hospitalized adult patients found that intermittent pneumatic compression was as effective as pharmacologic prophylaxis (with a RR=0.4) but with a decreased bleeding risk. It also showed efficacy in reducing the risk of PE with RR=0.48 *(Ho 2013 [1a])*.

In a small randomized control trial in adults, the use of intra-operative sequential compression device (SCD) has been shown to decrease venous stasis *(Schwenk 1998 [2b])*. These data support the local surgical consensus to use SCD in patients having surgeries lasting at least 60 minutes *(Local Consensus 2014 [5])*.

An adult study comparing SCD to graduated compression stockings (GCS) suggests SCD have superior efficacy in preventing DVT (RR=0.48) *(Arabi 2013 [3a])*. A large meta-analysis of hospitalized adult patients supports this finding *(Ho 2013 [1a])*.

Pharmacologic prophylaxis

Multiple adult studies support the benefit of heparin in reducing DVT. The RR of DVT in patients treated with heparin compared to no treatment is 0.51 [95%CI 0.41, 0.63; p<0.0001] *(Alhazzani 2013 [1a])* to 0.60 [95%CI 0.50, 0.71] *(Handoll 2002 [1a])*. LMWH may have a slight advantage to unfractionated heparin, as RR ranged from 0.68 to 0.9 in three meta-analyses, with significance demonstrated in two of the three *(Alhazzani 2013 [1a], Barrera 2013 [1a], Handoll 2002 [1a])*.

Head-to-head comparisons of pharmacological and mechanical prophylaxis in trauma patients show a possible slight advantage of pharmacological prophylaxis in preventing DVT [RR=0.48, 95%CI 0.25, 0.95] *(Barrera 2013 [1a])*.

At this time, there is insufficient evidence to recommend aspirin as prophylactic measure *(Falck-Ytter 2012 [5a], Gould 2012 [5a], Kahn 2012 [5a])*.

Efficacy of Combined Modalities

Meta-analyses of adult studies show that combining mechanical prophylaxis and pharmacologic prophylaxis lowers the overall risk of VTE compared to either single modality with RR ranging from 0.31 to 0.54 in four different types of comparisons, all statistically significant *(Barrera 2013 [1a], Ho 2013 [1a], Kakkos 2011 [1b])*.

Safety/Harm

Adverse event rates of SCD are low and generally minor. They include discomfort/intolerance & skin abrasions. Discomfort may lead to decreased adherence *(Handoll 2002 [1a])*.

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 one study that used twice a day dosing *(Bidlingmaier 2011 [1b])*. 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%). All four major bleeding events occurred in orthopedic patients *(Stem 2013 [3b])*. The American Society of Regional Anesthesia (ASRA) recommends waiting two hours after a traumatic catheter placement or removal and 12 hours after possibly traumatic catheter placement or removal prior to starting LMWH, to avoid the risk of hematoma *(Horlocker 2010 [5a])*.

Judging the strength of the recommendations

In determining the strength of the recommendation, the development group made a considered judgment in a consensus process which was reflective of critically appraised evidence, clinical experience, and these dimensions:

Given the dimensions below and that more answers to the left of the scales indicate support for stronger recommendations, the set of recommendations above reflect the strength of the set of recommendations as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Judging the strength of the recommendations for Assessing Risk: See Recommendation #2

1. Grade of the Body of Evidence	☐ High	☒ Moderate	☐ Low
Rationale: The assessment recommendation is based on studies of weak design, but the studies were in the pediatric population, numerous and the results consistent.			
2. Safety/Harm (Side Effects and Risks)	☒ Minimal	☐ Moderate	☐ Serious
Rationale: Risk assessment is easily obtained from a patient's history and therefore is non-invasive. It could be harmful if done incorrectly.			
3. Health benefit to patient	☐ Significant	☒ Moderate	☐ Minimal
Rationale: VTE incidence is increasing in the pediatric population *(Raffini 2009 [3a])* and there are no current guidelines in place to help identify those at risk. This risk stratification algorithm may help identify patients at high risk for VTE and decrease unnecessary prophylaxis measures in low risk patients.			
4. Burden to adhere to recommendation	☐ Low	☒ Unable to determine	☐ High
Rationale: The algorithm has not yet been tested in clinical scenarios. Use of the risk stratification algorithm may be limited by providers not being aware of its existence or disagreeing with the chosen risk factors.			
5. Cost-effectiveness to healthcare system	☐ Cost-effective	☒ Inconclusive	☐ Not cost-effective
Rationale: This was not assessed in our literature review or creation of this BESt statement.			
6. Directness of the evidence for this target population	☒ Directly relates	☐ Some concern of directness	☐ Indirectly relates
Rationale: The majority of the risk factors chosen were based on pediatric studies.			
7. Impact on morbidity/mortality or quality of life	☐ High	☐ Medium	☒ Low
Rationale: May theoretically decrease morbidity and mortality associated with VTE if patients are appropriately given thromboprophylaxis based on risk stratification, but this has not been studied in the pediatric population.			

Judging the strength of the recommendations for thromboprophylaxis: See Recommendations #1, 3 and 4

1. Grade of the Body of Evidence	☐ High	☐ Moderate	☒ Low
Rationale: The thromboprophylaxis recommendations are based on adult studies and local consensus.			
2. Safety/Harm (Side Effects and Risks)	☐ Minimal	☒ Moderate	☐ Serious
Rationale: Mechanical prophylaxis is associated with minimal risks. Pharmacologic prophylaxis carries a significant risk of bleeding.			
3. Health benefit to patient	☒ Significant	☐ Moderate	☐ Minimal
Rationale: VTE prophylaxis may prevent a life threatening event (pulmonary embolism) as well as chronic post-thrombotic syndrome.			
4. Burden to adhere to recommendation	☐ Low	☐ Unable to determine	☒ High
Rationale: Subcutaneous injections are painful for patients and required a skilled provider for administration. Appropriate mechanical prophylaxis requires patient and nurse effort.			
5. Cost-effectiveness to healthcare system	☐ Cost-effective	☒ Inconclusive	☐ Not cost-effective
Rationale: This was not assessed in our literature review or creation of this BESt statement.			
6. Directness of the evidence for this target population	☐ Directly relates	☐ Some concern of directness	☒ Indirectly relates
Rationale: Evidence for thromboprophylaxis is derived from studies conducted mostly on adult populations.			
7. Impact on morbidity/mortality or quality of life	☒ High	☐ Medium	☐ Low
Rationale: May prevent a life-threatening event and chronic health condition.			

Reference List *(Evidence Level in [ ]; See Table of Evidence Levels)*

1. **Alhazzani, W.; Lim, W.; Jaeschke, R. Z.; Murad, M. H.; Cade, J.; and Cook, D. J.:** Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med*, 41(9): 2088-98, 2013, [1a] http://www.ncbi.nlm.nih.gov/pubmed/23782973.

2. **Arabi, Y. M.; Khedr, M.; Dara, S. I.; Dhar, G. S.; Bhat, S. A.; Tamim, H. M.; and Afesh, L. Y.:** Use of Intermittent Pneumatic Compression and Not Graduated Compression Stockings Is Associated With Lower Incident VTE in Critically Ill Patients: A Multiple Propensity Scores Adjusted Analysis. *Chest*, 144(1): 152-9, 2013, [3a] http://www.ncbi.nlm.nih.gov/pubmed/23412593.

3. **Askegard-Giesmann, J. R.; O'Brien, S. H.; Wang, W.; and Kenney, B. D.:** Increased use of enoxaparin in pediatric trauma patients. *J Pediatr Surg*, 47(5): 980-3, 2012, [4a] http://www.ncbi.nlm.nih.gov/pubmed/22595585.

4. **Azu, M. C.; McCormack, J. E.; Scriven, R. J.; Brebbia, J. S.; Shapiro, M. J.; and Lee, T. K.:** Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? *J Trauma*, 59(6): 1345-9, 2005, [4b] http://www.ncbi.nlm.nih.gov/pubmed/16394907.

5. **Barrera, L. M.; Perel, P.; Ker, K.; Cirocchi, R.; Farinella, E.; and Morales Uribe, C. H.:** Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev*, 3: CD008303, 2013, [1a] http://www.ncbi.nlm.nih.gov/pubmed/23543562.

6. **Bidlingmaier, C.; Kenet, G.; Kurnik, K.; Mathew, P.; Manner, D.; Mitchell, L.; Krumpel, A.; and Nowak-Gottl, U.:** Safety and efficacy of low molecular weight heparins in children: a systematic review of the literature and meta-analysis of single-arm studies. *Semin Thromb Hemost*, 37(7): 814-25, 2011, [1b] http://www.ncbi.nlm.nih.gov/pubmed/22187405.

7. **Branchford, B.; Wang, M.; Wathen, B.; Ranade, D.; Neiman, J.; Coughlin, R.; Pickard, D.; and Children's Hospital of Colorado:** *Unpublished document*. Clinical Care Guideline: VTE Prophylaxis 2012 [5b] **E**.

8. **Branchford, B. R.; Mourani, P.; Bajaj, L.; Manco-Johnson, M.; Wang, M.; and Goldenberg, N. A.:** Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. *Haematologica*, 97(4): 509-15, 2012, [4a] http://www.ncbi.nlm.nih.gov/pubmed/22133768.

9. **Candrilli, S. D.; Balkrishnan, R.; and O'Brien, S. H.:** Effect of injury severity on the incidence and utilization-related outcomes of venous thromboembolism in pediatric trauma inpatients. *Pediatric Critical Care Medicine*, 10(5): 554-557, 2009, [3a (incidence); 4a (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/19451844.

10. **Coleridge-Smith, P. D.; Hasty, J. H.; and Scurr, J. H.:** Venous stasis and vein lumen changes during surgery. *Br J Surg*, 77(9): 1055-9, 1990, [5] http://www.ncbi.nlm.nih.gov/pubmed/2207573.

11. **Cyr, C.; Michon, B.; Pettersen, G.; David, M.; and Brossard, J.:** Venous thromboembolism after severe injury in children. *Acta Haematol*, 115(3-4): 198-200, 2006, [3b (incidence); 4b (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/16549896.

12. **Falck-Ytter, Y. et al.:** Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 141(2 Suppl): e278S-325S, 2012, [5a] http://www.ncbi.nlm.nih.gov/pubmed/22315265.

13. **Galson, S. K., and The U.S. Department of Health and Human Services:** The Surgeon General's call to action to prevent deep vein thrombosis and pulmonary embolism. Report for *Call to Action*: 1-49, 2008, [5] http://www.surgeongeneral.gov/library/calls/deepvein/call-to-action-on-dvt-2008.pdf .

14. **Gould, M. K.; Garcia, D. A.; Wren, S. M.; Karanicolas, P. J.; Arcelus, J. I.; Heit, J. A.; Samama, C. M.; and American College of Chest, P.:** Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 141(2 Suppl): e227S-77S, 2012, [5a] http://www.ncbi.nlm.nih.gov/pubmed/22315263.

15. **Grandas, O. H.; Klar, M.; Goldman, M. H.; and Filston, H. C.:** Deep venous thrombosis in the pediatric trauma population: an unusual event: report of three cases. *Am Surg*, 66(3): 273-6, 2000, [4b] http://www.ncbi.nlm.nih.gov/pubmed/10759198.

16. **Greenwald, L. J.; Yost, M. T.; Sponseller, P. D.; Abdullah, F.; Ziegfeld, S. M.; and Ain, M. C.:** The role of clinically significant venous thromboembolism and thromboprophylaxis in pediatric patients with pelvic or femoral fractures. *J Pediatr Orthop*, 32(4): 357-61, 2012, [4a] http://www.ncbi.nlm.nih.gov/pubmed/22584835.

17. **Handoll, H. G. H.; Farrar, M. J.; McBirnie, J.; Tytherleigh-Strong, G. M.; Milne, A. A.; and Gillespie, W. J.:** Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev*, (4), 2002, [1a].

18. **Hanson, S. J.; Punzalan, R. C.; Arca, M. J.; Simpson, P.; Christensen, M. A.; Hanson, S. K.; Yan, K.; Braun, K.; and Havens, P. L.:** Effectiveness of clinical guidelines for deep vein thrombosis prophylaxis in reducing the incidence of venous thromboembolism in critically ill children after trauma. *J Trauma Acute Care Surg*, 72(5): 1292-7, 2012, [4b] http://www.ncbi.nlm.nih.gov/pubmed/22673257.

19. **Hanson, S. J.; Punzalan, R. C.; Greenup, R. A.; Liu, H.; Sato, T. T.; and Havens, P. L.:** Incidence and risk factors for venous thromboembolism in critically ill children after trauma. *J Trauma*, 68(1): 52-6, 2010, [2a (incidence); 3a (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/20065757.

20. **Ho, K. M., and Tan, J. A.:** Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation*, 128(9): 1003-20, 2013, [1a] http://www.ncbi.nlm.nih.gov/pubmed/23852609.

21. **Horlocker, T. T. et al.:** Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*, 35(1): 64-101, 2010, [5a] http://www.ncbi.nlm.nih.gov/pubmed/20052816.

22. **Kahn, S. R. et al.:** Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 141(2 Suppl): e195S-226S, 2012, [5a] http://www.ncbi.nlm.nih.gov/pubmed/22315261.

23. **Kakkos, S. K.; Caprini, J. A.; Geroulakos, G.; Nicolaides, A. N.; Stansby, G. P.; Tsolakis, I. A.; and Reddy, D. J.:** Can combined (mechanical and pharmacological) modalities prevent fatal VTE? *Int Angiol*, 30(2): 115-22, 2011, [1b] http://www.ncbi.nlm.nih.gov/pubmed/21427647.

24. **Local Consensus:** During guideline development timeframe. 2014, [5].

25. **Michota, F. A.:** Bridging the gap between evidence and practice in venous thromboembolism prophylaxis: the quality improvement process. *J Gen Intern Med*, 22(12): 1762-70, 2007, [5] http://www.ncbi.nlm.nih.gov/pubmed/17891516.

26. **Monagle, P.; Chan, A. K.; Goldenberg, N. A.; Ichord, R. N.; Journeycake, J. M.; Nowak-Gottl, U.; Vesely, S. K.; and American College of Chest Physicians:** Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 141(2 Suppl): e737S-801S, 2012, [5a] http://www.ncbi.nlm.nih.gov/pubmed/22315277.

27. **O'Brien, S. H., and Candrilli, S. D.:** In the absence of a central venous catheter, risk of venous thromboembolism is low in critically injured children, adolescents, and young adults: evidence from the National Trauma Data Bank. *Pediatr Crit Care Med*, 12(3): 251-6, 2011, [3a (incidence); 4a (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/20921921.

28. **Raffini, L.; Huang, Y. S.; Witmer, C.; and Feudtner, C.:** Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*, 124(4): 1001-8, 2009, [3a] http://www.ncbi.nlm.nih.gov/pubmed/19736261.

29. **Raffini, L.; Trimarchi, T.; Beliveau, J.; and Davis, D.:** Thromboprophylaxis in a pediatric hospital: a patient-safety and quality-improvement initiative. *Pediatrics*, 127(5): e1326-32, 2011, [5b] http://www.ncbi.nlm.nih.gov/pubmed/21464186.

30. **Rana, A. R.; Michalsky, M. P.; Teich, S.; Groner, J. I.; Caniano, D. A.; and Schuster, D. P.:** Childhood obesity: a risk factor for injuries observed at a level-1 trauma center. *J Pediatr Surg*, 44(8): 1601-5, 2009, [4a] http://www.ncbi.nlm.nih.gov/pubmed/19635312.

31. **Schwenk, W.; Bohm, B.; Fugener, A.; and Muller, J. M.:** Intermittent pneumatic sequential compression (ISC) of the lower extremities prevents venous stasis during laparoscopic cholecystectomy. A prospective randomized study. *Surg Endosc*, 12(1): 7-11, 1998, [2b] http://www.ncbi.nlm.nih.gov/pubmed/9419295.

32. **Sharathkumar, A. A.; Mahajerin, A.; Heidt, L.; Doerfer, K.; Heiny, M.; Vik, T.; Fallon, R.; and Rademaker, A.:** Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-Clot clinical Decision Rule. *J Thromb Haemost*, 10(7): 1326-34, 2012, [4a] http://www.ncbi.nlm.nih.gov/pubmed/22583578.

33. **Stein, P. D.; Kayali, F.; and Olson, R. E.:** Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. *J Pediatr*, 145(4): 563-5, 2004, [3a] http://www.ncbi.nlm.nih.gov/pubmed/15480387.

34. **Stem, J.; Christensen, A.; Davis, D.; and Raffini, L.:** Safety of prophylactic anticoagulation at a pediatric hospital. *J Pediatr Hematol Oncol*, 35(7): e287-91, 2013, [3b] http://www.ncbi.nlm.nih.gov/pubmed/23774158.

35. **Takemoto, C. M. et al.:** Hospital-Associated Venous Thromboembolism in Children: Incidence and Clinical Characteristics. *J Pediatr*, 2013, [4a] http://www.ncbi.nlm.nih.gov/pubmed/24332452.

36. **Truitt, A. K.; Sorrells, D. L.; Halvorson, E.; Starring, J.; Kurkchubasche, A. G.; Tracy, T. F., Jr.; and Luks, F. I.:** Pulmonary embolism: which pediatric trauma patients are at risk? *J Pediatr Surg*, 40(1): 124-7, 2005, [3a (incidence); 4a (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/15868571.

37. **Vavilala, M. S.; Nathens, A. B.; Jurkovich, G. J.; Mackenzie, E.; and Rivara, F. P.:** Risk factors for venous thromboembolism in pediatric trauma. *J Trauma*, 52(5): 922-7, 2002, [3a (incidence); 4a (risk factors)] http://www.ncbi.nlm.nih.gov/pubmed/11988660.

38. **Vu, L. T.; Nobuhara, K. K.; Lee, H.; and Farmer, D. L.:** Determination of risk factors for deep venous thrombosis in hospitalized children. *J Pediatr Surg*, 43(6): 1095-9, 2008, [4a] http://www.ncbi.nlm.nih.gov/pubmed/18558189.

39. **Wright, J. M., and Watts, R. G.:** Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. *J Pediatr Hematol Oncol*, 33(4): 261-4, 2011, [4a] http://www.ncbi.nlm.nih.gov/pubmed/21516021.

IMPLEMENTATION

Applicability & Feasibility Issues

There is evidence that VTE events are increasing in the pediatric population *(Raffini 2009 [3a])*, and it has become evident to many providers, including medical and surgical specialists, that we must do a better job of prevention. These care recommendations provide a means to assess patients at risk and mitigate that risk in the safest possible way. As the recommendations are newly developed, the feasibility of implementation has as yet been untested. Generally, we believe implementation efforts will need to address:

1. education and training of staff to perform the risk assessment and review of contraindications, and to order prophylaxis;
2. identifying an appropriate time and place during the hospitalization to apply the recommendations;
3. ensuring adequate equipment and supplies; and
4. successfully achieving patient and family buy-in.

A tool in the electronic health record (EHR) may need to be developed to improve reliable use of the recommendations.

Relevant CCHMC Tools

P&T Committee Consensus Guideline: Low Molecular Weight Heparin Dosing and Monitoring Guideline
Health topic: Enoxaparin (Lovenox): http://www.cincinnatichildrens.org/patients/child/encyclopedia/treat/pharma/enoxaparin/
Knowing Notes: http://centerlink.cchmc.org/content2/46794/
Deep Venous Thrombosis (DVT)
Pulmonary Embolism (PE)
Anticoagulation "Blood Thinning" Medicines
No policies or procedures were found.

Outcome Measures and Process Measures

The global aim of this effort is to decrease hospital-acquired VTE events. Incidence of VTE in the overall pediatric inpatient population is not well known; local surveillance data would be useful as a global outcome measure.

Suggested process measures are:

1. Successful preoperative patient assessment with appropriate application of recommended SCD prophylaxis for surgical patients.
2. Risk assessment and application of recommended prophylaxis for all eligible patients at time of admission.
3. Risk assessment and application of recommended prophylaxis at 48 to 72 hours of hospitalization.

Each of these measures represents an essential component of the recommended algorithm.

Alternative outcomes that may be considered include measures of family engagement and satisfaction with the successful implementation of this algorithm.

Algorithm: Risk Category Assessment and Prophylaxis for Venous Thromboembolism

Definitions, abbreviations and development credit for the algorithm – See next page

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?

No → Other risk factors?*
- No → Low risk
- Yes → Moderate risk

Yes → # of other risk factors?*
- One or less → Moderate risk
- Two or more → High risk

High risk → Anticoagulation contraindicated?***
- Yes → Intervention
- No → Intervention

Intervention:
• Encourage early ambulation and • Mitigate risk factors

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

AND
- Consider pharmacologic prophylaxis
- Obtain hematology consult when weighing risk benefit in patients at risk of bleeding

Low Molecular Weight Heparin Dosing and Monitoring Guideline *(internal CCHMC document)*

If decision to initiate pharmacologic prophylaxis:
- in surgical patients seek surgical input regarding bleeding risk, prior to initiation
- see CCHMC P&T Committee Consensus Guideline for management of LMWH prophylaxis
- obtain hematology consult when considering alternative pharmacologic agents

Reassess risk at 48 to 72 hours of hospitalization

***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/mm^3

Relative:
Intracranial mass
Lumbar puncture or epidural catheter removal in prior 12 hours
Neurosurgical procedure
Pelvic fracture within past 48 hours
Uncontrolled hypertension

Definitions and Abbreviations for Algorithm

Altered Mobility	○ A permanent or temporary state in which the child has a limitation in independent, purposeful physical movement of the body or of one or more extremities		
Risk Category			
Low Risk	○ No VTE risk factors		
Moderate Risk	○ Multiple risk factors for VTE in the absence of altered mobility or has altered mobility with one or fewer additional risk factors		
High Risk	○ Altered mobility plus two or more additional risk factors		
Abbreviations	○ BMI = body mass index ○ DVT = deep vein thrombosis ○ GCS = graduated compression stockings ○ hrs = hours ○ IBD = inflammatory bowel disease	○ LMWH = low molecular weight heparin ○ mm^3 = cubic millimeters ○ mOsm/kg = milliOsmoles per kilogram ○ PICC = peripherally-inserted central catheter	○ PIV = peripheral intravenous ○ SCD = sequential compression device ○ SLE = systemic lupus erythematosus ○ VTE = venous thromboembolism

This algorithm was adapted from a draft created at Children's Hospital of Colorado; permission was granted from the first author for this endeavor *(Branchford 2012 [5b])*.

SUPPORTING INFORMATION

Background/Purpose of BESt Development

Venous thromboembolism (VTE) has become increasingly recognized as a significant public health burden, particularly hospital-acquired VTE *(Raffini 2009 [3a])*. In recent years there have been a number of initiatives aimed at increasing awareness and prevention issued by organizations such as the Joint Commission on Accreditation for Healthcare Organizations and the Surgeon General *(Galson 2008 [5], Michota 2007 [5])*. Although the incidence of venous thromboembolism in children is considerably lower (estimated at 5 per 10,000 from National Discharge Survey *(Stein 2004 [3a])*) than in adults, there is some evidence that the incidence is rapidly increasing (as high as 58 per 10,000 in 2007 compared to 34 per 10,000 in 2001 *(Raffini 2009 [3a])*). Rates in pediatric trauma patients are even higher (retrospective studies of high risk cases demonstrate rates of 60 to 100 per 10,000 *(O'Brien 2011 [3a (incidence); 4a (risk factors)], Vavilala 2002 [3a (incidence); 4a (risk factors)], Askegard-Giesmann 2012 [4a])*; one small prospective study reported 620 per 10,000 *(Hanson 2010 [2a (incidence); 3a (risk factors)])*. Consequences of VTE are significant, including pulmonary embolism (found in 16 to 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) *(Branchford 2012 [4a])*.

There are already well-established guidelines for risk stratification and prophylaxis in the adult population but there is a growing need for similar protocols in pediatrics. Such guidelines are particularly important as tertiary institutions like CCHMC care for growing populations of medically complex patients and young adults.

Therefore, a multidisciplinary taskforce comprised of physicians from pediatric hematology, pediatric critical care, pediatric orthopaedics, pediatric general and trauma surgery and pediatric hospital medicine along with a methodologist from the James M. Anderson Center of Excellence was established. The aim of this taskforce was to develop care recommendations for VTE prophylaxis in children and adolescents.

Of note, multiple pediatric studies observed a bimodal age distribution in hospital-acquired VTE, with peaks occurring in infancy and adolescence *(Takemoto 2013 [4a], Branchford 2012 [4a], Raffini 2011 [5b])*. Our taskforce did not include infants in the algorithm because this population is outside of our taskforce's scope of expertise and thromboprophylaxis has not been well studied in this age group.

Definitions for the recommendations, tables and text

altered mobility: a permanent or temporary state in which the child has a limitation in independent, purposeful physical movement of the body or of one or more extremities

deep vein thrombosis (DVT): a blood clot (thrombus) that was initially formed in a deep (non-peripheral) vein

graduated compression stockings (GCS): elastic stockings (ES), either knee- or thigh-high, also known as TED stockings

major bleeding: as defined by the International Society of Hemostasis and Thrombosis – fatal bleeding, overt bleeding with hemoglobin drop of ≥ 2grams/deciLiter in 24 hours, bleeding into a critical organ (brain, lung, retroperitoneal), or bleeding requiring surgical intervention

mechanical prophylaxis: any one of several methods to assist the flow of blood in the deep veins of the leg and includes graduated compression stockings, sequential compression devices and foot pumps

minor bleeding: as defined by the International Society of Hemostasis and Thrombosis – overt or macroscopic bleeding that does not meet criteria for major bleeding

sequential compression device (SCD): a device designed to intermittently squeeze blood from underlying deep veins in the leg upon compression of an inflatable sleeve, and to allow the blood to flow again when it decompresses; also known as intermittent compression device (ICD) or intermittent pneumatic compression (IPC)

venous thromboembolism (VTE): a blood clot (thrombus) in a vein or one that has broken free and is carried in the bloodstream (embolus)

Search Strategies

Iterative searches were conducted in the course of the development of this document.

Search 1: VTE prophylaxis in pediatric trauma and orthopaedic patients
Databases: Medline, Cochrane Database of Systematic Reviews (CDSR), CINAHL
Terms: various terms for VTE (VTE, DVT, PE, thrombosis, venous thrombosis, thromboembolism, deep vein thrombosis, pulmonary embolism)
AND various terms for trauma or orthopaedic surgery (trauma, wounds, injuries, orthopedic)
AND various terms for VTE prophylaxis (enoxaparin, heparin, anticoagulants fibrinolytic agents, prophylaxis combined with thrombus or embolus)
Filters: publication dates 2000 to present; pediatric studies only; English language
Date: search was conducted: November 14, 2012; update of search conducted January 13, 2014

Search 2: Adverse events with VTE prophylaxis in hospitalized children
Databases: Medline Cochrane, CINAHL, Scopus, EBMR
Terms: various terms for VTE prophylaxis (enoxaparin, heparin, anticoagulants fibrinolytic agents, prophylaxis combined with thrombus or embolus)
AND various terms for adverse events (hemorrhage, bleeding, risk of bleeding, adverse effect, adverse event)
Filters: publication dates 2000 to present; pediatric studies only; English language
Date search was conducted: January 24, 2013; update of search conducted January 13, 2014

Search 3: Mechanical Prophylaxis of VTE
Databases: Medline, Scopus, CINAHL, CDSR
Terms: various terms for VTE (VTE, DVT, PE, thrombosis, venous thrombosis, thromboembolism, deep vein thrombosis, pulmonary embolism)
AND various terms for mechanical prophylaxis (intermittent compression device, mechanical prophylaxis, sequential compression device, foot pump, pneumatic compression, graduated compression stocking, TED stockings, elastic compression stockings)
Filters: no limits on patient age or on publication dates; English language
Date: search was conducted: February 26, 2013; update of search conducted January 13, 2014

Search 4: Definitions of Immobilization
Database: Medline
Terms: various terms for VTE (VTE, DVT, PE, thrombosis, venous thrombosis, thromboembolism, deep vein thrombosis, pulmonary embolism) AND various terms for immobilization (immobility, bed rest, bedridden, confined to bed)
Filters: no limits on publication dates; pediatric studies or meta-analyses of adult studies; English language
Date: search was conducted: May 2, 2013; update of search conducted January 13, 2014

In addition, articles identified by members of the team and relevant articles from reference lists were considered.

Group/Team Members

Leader/Co-Author: Erin Shaughnessy, MD, Pediatric Hospital Medicine
Co-Authors: Katie Meier, MD, Pediatric Hospital Medicine
Eloise Clark, MPH, MBA, Methodologist
Contributors: Cristina Tarango, MD, Pediatric Hematology
Ranjit Chima, MD, Pediatric Critical Care
Rebeccah Brown, MD, Pediatric Surgery
Jaime Rice Denning, MD, Pediatric Orthopaedic Surgery
Joel Sorger, MD, Pediatric Orthopaedic Surgery

Conflicts of Interest were declared for each team member and:

☒ No financial or intellectual conflicts of interest were found.
☐ The following conflicts of interest were disclosed:

Note: Full tables of the LEGEND evidence evaluation system are available in separate documents:

- *Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)*
- *Grading a Body of Evidence to Answer a Clinical Question*
- *Judging the Strength of a Recommendation (dimensions table below and Rationale)*

Table of Evidence Levels *(see note above)*:

Quality level	***Definition***
1a† or 1b†	*Systematic review, meta-analysis, or meta-synthesis of multiple studies*
2a or 2b	*Best study design for domain*
3a or 3b	*Fair study design for domain*
4a or 4b	*Weak study design for domain*
5a or 5b	*General review, expert opinion, case report, consensus report, or guideline*
5	*Local Consensus*

†a = good quality study; b = lesser quality study

Table of Language and Definitions for Recommendation Strength *(see note above)*:

Language for Strength	***Definition***
It is strongly recommended that… *It is strongly recommended that… not…*	*When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly outweigh risks and burdens. (or visa-versa for negative recommendations)*
It is recommended that… *It is recommended that… not…*	*When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.*
There is insufficient evidence and a lack of consensus to make a recommendation…	

Please cite as: Multidisciplinary VTE Prophylaxis BESt Team, Cincinnati Children's Hospital Medical Center: Best Evidence Statement Venous Thromboembolism (VTE) Prophylaxis in Children and Adolescents, http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/bests/, BESt 181, pages 1-14, Date 2/18/14.

This Best Evidence Statement has been reviewed against quality criteria by two independent reviewers from the CCHMC Evidence Collaboration. Conflict of interest declaration forms are filed with the CCHMC EBDM group.
The BESt will be removed from the Cincinnati Children's website, if content has not been revised within five years from the most recent publication date. A revision of the BESt may be initiated at any point that evidence indicates a critical change is needed.

Review History

Date	*Event*	*Outcome*
2/18/2014	**Original Publication**	New BESt developed and published

For more information about CCHMC Best Evidence Statements and the development process, contact the Evidence Collaboration at EBDMinfo@cchmc.org.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.