RECOMMENDATIONS AND GUIDELINES

# Recommendations for standardized risk factor definitions in pediatric hospital-acquired venous thromboembolism to inform future prevention trials: communication from the SSC of the ISTH

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## Background

The incidence of pediatric hospital-associated venous thromboembolism (HA-VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) occurring during hospitalization or within 30 days of discharge, is rising [1]. This increase is attributed to increased utilization of aggressive life-saving measures in the intensive care unit (ICU) that necessitate the use of central venous catheters (CVCs), as well as increased clinical awareness and better recognition with advanced diagnostic techniques [2]. This rise in pediatric HA-VTE cases prompts concern over increased co-morbidities (e.g. post-thrombotic syndrome), mortality and financial burden. Guidelines on safe and effective strategies to prevent pediatric HA-VTE are therefore imperative.

Unfortunately, pediatric HA-VTE prevention guidelines are not well established, mainly because of a paucity of evidence in this population, even though children may share risk factors with adult patients [3–6]. Pediatric HA-VTE risk factor data are available from a few small, single-institution studies [3,7,8], but lack sufficient power to discern differences across important subgroups such as types of surgery (e.g. orthopedic vs. neurosurgery) or cancer (e.g. leukemia vs. solid tumors). Consistent risk factor definitions, needed for reliable interpretation of studies from different research groups such as these, are lacking. Moreover, pediatric VTE pathophysiology is different from that of adults, particularly concerning the role of CVCs, which are present in the majority of pediatric HA-VTE patients [9–11].

A recent systematic literature review and meta-analysis of risk factors and risk assessment models [12] was performed by our Working Group for Pediatric HA-VTE Prevention and Risk Scores. This review confirmed the presence of a CVC, ICU admission, mechanical ventilation and length of hospitalization as important risk factors for pediatric HA-VTE [10]. Unfortunately, the meta-analysis was limited (primarily by lack of agreement in risk factor definitions) to 60 articles from nearly 400 that were initially identified. Additionally, work has recently begun on differentiating risk factors among children in

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different hospital units, as it is expected that non-critically-ill children [13] may exhibit different HA-VTE risk profiles to those in pediatric [14], cardiac [15] or neonatal [16] ICUs. Prevention strategies may also differ by age group [17,18].

## Rationale

A few single-institution studies have demonstrated risk models [3,4,7,13], but more work is needed to develop an accurate risk-adapted scoring system. Pediatric-specific HA-VTE risk factor definitions and outcomes must be standardized to allow for consistency among future prospectively validated risk models as a basis for risk-stratified prevention trials.

## Methods

The recommendations herein summarize expert consensus, including presentations and discussions at the Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee meetings during the 60th and 61st Scientific and Standardization Committee (SSC) meetings of the International Society on Thrombosis and Haemostasis (ISTH). A Working Group for 'Pediatric HA-VTE Prevention and Risk Scores' comprising N.A. Goldenberg (Chairman), B.R. Branchford, A. Mahajerin, L. Raffini, E. Chalmers and C. H. van Ommen was assembled. Key source materials included a recent systematic review of the pediatric HA-VTE literature [10]. Final recommendations were derived by consensus from subject matter experts and include input from former and current Subcommittee Chairmen, A.K.C. Chan and C. Male, respectively.

### *Recommendations*

*Recommendation 1: Risk Factor Definitions* This Working Group was convened to address risk factor definition standardization, but also emphasizes several overall considerations for future pediatric HA-VTE research. Table 1 displays suggested standardized definitions for some risk factors (from prior single-institution studies) with historically variable meanings.

1A: Risk factor duration. In general, risk factor definitions should include the duration (e.g. CVCs by catheter-in-situ days or hormone replacement therapy/contraception by length of therapy prior to symptom onset) needed for them to be considered 'provoking', as well as an assessment of whether the factor is modifiable.

1B: CVC-specific considerations. Because CVCs are so commonly associated with pediatric HA-VTE, it is important to clearly define CVC-specific features, including line type, material, insertion site and tip location. Additionally, CVC insertion increasingly utilizes ultrasound guidance to decrease insertion attempts and more accurately estimate the catheter to vessel diameter ratio, decreasing endothelial injury events and mechanical flow restriction, respectively. Identification of the characteristics most highly associated with CVC-related VTE will be critical to future risk stratification and mitigation strategies.

*Recommendation 2: Study Design and Endpoints* Prior ISTH SSC guidelines exist for VTE clinical anticoagulation trials evaluating safety and efficacy, but those designed to address prevention may warrant different endpoints. Risk factor studies should prioritize symptomatic VTE but should also consider non-invasive surveillance for asymptomatic VTE events as a secondary endpoint. Because poor sensitivity and specificity of discharge diagnosis codes from the International Classification of Diseases, $9^{th}$ edition (ICD-9) for VTEs have been described [19–21], putative VTE cases retrospectively identified via billing codes should be diagnostically validated via radiologic report.

The Working Group also recommends addressing the obstacle of small patient numbers by prioritizing collaborative, multi-institutional studies to increase enrollment ability and dilute regional differences in underlying medical co-morbidities. These studies will ideally have a nested case–control design (i.e. random selection of controls from all inpatients in an institution, to decrease bias resulting from control group choice), as the odds ratios and multivariate logistic regression available in this context allow for rank-ordering of risk factors. Graded risk scores can then be created by retrospective chart review and later prospectively validated in cohort studies and, ultimately, randomized control trials to evaluate safety and efficacy of intervention strategies.

*Recommendation 3: Clinical Subgroup Focus* Finally, the Working Group also recommends that future pediatric HA-VTE efforts focus on delineation of specific clinical subgroups to aid in appropriate risk stratification to guide safe and effective thromboprophylaxis efforts.

In particular, greater emphasis on age stratification is needed, as it has been demonstrated that the risk of VTE varies considerably across patient age, with the highest incidence during the neonatal period, followed by another peak in adolescence [22,23]. Studies should, therefore, report the distribution of data by age, including neonates (0–30 days), infants (> 30 days–1 year), pre-school children (1–5 years), school-aged children (5–12 years) and adolescents (12–18 years). Also, more clinical risk factor subgroups should be considered (e.g. medical vs. surgical patients, critically ill vs. non-critically ill, solid tumor vs. leukemia, and surgery types and durations).

## Discussion

A recent systematic review of the pediatric HA-VTE literature [10] encapsulated many of the obstacles to high-quality pediatric VTE research: a small overall number of

**Table 1** Definitions of terminology

| Risk factor | Definition | Notes |
|---|---|---|
| VTE | PE, DVT affecting venous drainage from limbs (including intra-abdominal thrombosis), right atrial thrombosis, cerebral sinus venous thrombosis<br>Does not include catheter tip fibrin sheath, or clots in external circulation devices (extra-corporeal membrane oxygenation, ventricular assist device, etc.) | Not present or suspected on admission<br>Subgroup analysis by VTE location and character (symptomatic/asymptomatic, occlusive/non-occlusive, etc.) suggested when numbers permit<br>Personal history of VTE defined as prior deep vein thrombosis or pulmonary embolism in the subject |
| Central venous catheter (CVC) | Intravascular catheter terminating at or close to the heart or in one of the great vessels, used for delivery of fluids or medications, hemodialysis, hemodynamic monitoring or frequent blood draws | Clarify short term (e.g. peripherally inserted central catheter, temporary jugular or femoral line) or long term (e.g. mediport, broviac or other tunneled CVC) |
| Immobility | Mobility decreased from baseline for > 48 h, including, but not limited to, that resulting from sedation for mechanical ventilation, acute spinal injury, transverse myelitis or Guillain-Barre syndrome | Differentiate severe immobility (ICU admission or bedrest order) from minimal (no restrictions) and moderate (remaining clinical situations)<br>May consider inability to ambulate 100 feet without support [31] or Braden Q Mobility Score < 2 ('very limited or completely immobile') or Activity Score < 2 ('chairfast' or 'bedfast') [32] |
| Cancer | Active cancer (i.e. not in remission for leukemia/lymphoma or not having undergone local control for solid tumors) | Differentiate solid tumor from leukemia/lymphoma, phase of therapy, type of chemotherapy used (e.g. asparaginase, steroids), and type of CVC used |
| Infection | Systemic or severe local infections. Positive blood/sputum culture, blood/respiratory viral assay, imaging study (pneumonia, mastoiditis) or systemic antibiotics | |
| Weight | Morbid obesity (body mass index [BMI] > 99th percentile for age), obesity (> 95–99th percentile) and overweight (85–95th percentile) | BMI valid for patients 2–20 years<br>When evaluating as a dichotomous variable based on an informative threshold, also report distribution of data and analyze also as a continuous variable |
| Pregnancy | 12 weeks post-conception through to 6 weeks post-partum | |
| Inflammation | Systemic inflammatory response syndrome or acute exacerbation of inflammatory disease (cystic fibrosis, inflammatory bowel disease, juvenile idiopathic arthritis, systemic lupus erythematosus, sickle cell disease with vaso-occlusive crisis, etc.), severe burns | C-reactive protein, erythrocyte sedimentation rate, D-dimer, interleukin-6, procalcitonin, ferritin |
| Length of stay | Hospital days | When evaluating as a dichotomous variable based on an informative threshold, also report distribution of data and analyze also as a continuous variable |
| Decreased natural anticoagulants | Loss {nephrotic syndrome, protein-losing enteropathy, asparaginase (48 h effect, or 14 days for pegylated version [33])} or consumption (disseminated intravascular coagulation, purpura fulminans, meningococcal infections, etc.) | |
| Surgery | Operative procedure (with general anesthesia) requiring subsequent hospital admission or occurring during a hospitalization or within the prior 2 weeks | Surgical subgroups (orthopedic spine, orthopedic non-spine, general/abdominal, neurosurgical, etc.) should be considered separately Track anesthesia time<br>Note if admission to surgery service for specific diagnosis of injury, and report the Injury Severity Score (ISS [34]) |
| Family history | Venous or arterial thrombotic event in first-degree relative before age 40 years<br>Multiple unexplained spontaneous abortions<br>Severe thrombophilia in first-degree relative (deficiencies of antithrombin, protein C or protein S according to age-based normals), homozygous/compound heterozygote mutations of prothrombin (G20210A mutation) or factor V (Leiden mutation) | |
| Moderate/severe dehydration (by World Health Organization definition) | Moderate (2 of the following): thirst, restless/irritable behavior, slight decrease in skin turgor<br>Severe (2 of following): lethargic/unconscious, poor drinking or inability to drink, lack of urine output, sunken eyes, major decrease in skin turgor | Because hemoconcentration increases blood viscosity, future studies should quantify this state to afford a widely applicable assessment of its significance |

studies (mostly retrospective case series, registry reviews or cohort studies with small patient numbers) and marked variability in the definitions of various risk factors. Some of these risk factors are quite difficult to define, but the Working Group has made suggestions in Recommendations above.

Unlike some hospital-acquired conditions such as central line-associated blood stream infections, in which the targeted interventions (e.g. sterile technique for line access) are benign, thromboprophylaxis for HA-VTE prevention carries potential risks of pressure ulcers (mechanical) and bleeding (pharmacologic). Although the risk of major bleeding [24] with prophylactic anticoagulation dosing is likely to be quite small, based on the low rate (~2%) reported for therapeutic dosing levels in adult studies [25] it still may complicate the decision to institute this strategy. Other practical barriers include cost, discomfort with injections, and various medication options [26,27].

Detailed information on the risk of HA-VTE in specific patient subgroups will inform risk-based interventions and decrease unnecessary exposure to interventions with potential adverse effects. This consideration becomes particularly noteworthy in certain subpopulations, such as children with cancer with a risk of bleeding from chemotherapy-related thrombocytopenia or other coagulation defects that outweighs the potential benefit of pharmacologic thromboprophylaxis [28].

The field currently lacks high-quality risk factor data in pediatric HA-VTE. Therefore, a main priority is to design studies to validate existing risk scores via multicenter retrospective (e.g. case–control) and prospective (e.g. hospital-based observational cohort, with nested case–control design) studies. Large collaborative studies or database mining (such as those regarding pediatric trauma [12,29,30]) are needed to generate adequate power to mitigate the high confounding potential of myriad putative risk factors in light of relatively rare pediatric HA-VTE events. These studies should prioritize the evaluation of significant risk factors identified in a recent systematic literature review [10]: presence of CVC, ICU admission, mechanical ventilation and prolonged admission. Once informed by risk stratification from cooperative observational studies, multicenter randomized control trials of mechanical and/or pharmacologic thromboprophylaxis should be instituted to evaluate whether risk-assessment and risk-based intervention strategies are both safe and effective in reducing the incidence of pediatric HA-VTE in specific patient subgroups. Such recommendations are the objective of future efforts by the Working Group. Additionally, although it is beyond the scope of the present communication, it is worthwhile noting that although the Working Group focused on standardizing definitions of VTE clinical research elements, it also discussed the importance of common-sense approaches to prevention of VTE (e.g. using established central line-associated bloodstream infection prevention efforts to also reduce the incidence of VTE, optimizing CVC to vessel diameter ratios and insertion techniques, and early mobilization).

## Addendum

B. Branchford wrote the original draft of the manuscript, which was then reviewed and edited by A. Mahajerin, L. Raffini, E. Chalmers, and C. H. van Ommen before final review by the Working Group Chair, N. Goldenberg. The SSC Chair, A. K. C. Chan, then solicited feedback from the whole committee prior to submission of the final version.

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## Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

## References

1 Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics* 2009; **124**: 1001–8.
2 Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA Jr. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; **371**: 387–94.
3 Branchford BR, Mourani P, Bajaj L, Manco-Johnson M, Wang M, Goldenberg NA. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. *Haematologica* 2012; **97**: 509–15.
4 Hanson SJ, Punzalan RC, Greenup RA, Liu H, Sato TT, Havens PL. Incidence and risk factors for venous thromboembolism in critically ill children after trauma. *J Trauma* 2010; **68**: 52–6.
5 Sandoval JA, Sheehan MP, Stonerock CE, Shafique S, Rescorla FJ, Dalsing MC. Incidence, risk factors, and treatment patterns for deep venous thrombosis in hospitalized children: an increasing population at risk. *J Vasc Surg* 2008; **47**: 837–43.
6 Wright JM, Watts RG. Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. *J Pediatr Hematol Oncol* 2011; **33**: 261–4.
7 Sharathkumar AA, Mahajerin A, Heidt L, Doerfer K, Heiny M, Vik T, Fallon R, 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* 2012; **10**: 1326–34.
8 Prentiss AS. Early recognition of pediatric venous thromboembolism: a risk-assessment tool. *Am J Crit Care* 2012; **21**: 178–83.
9 Jaffray J, Bauman M, Massicotte P. The impact of central venous catheters on pediatric venous thromboembolism. *Front Pediatr* 2017; **5**: 5.

10 Mahajerin A, Branchford BR, Amankwah EK, Raffini L, Chalmers E, van Ommen CH, Goldenberg NA. Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models. *Haematologica* 2015; **100**: 1045–50.

11 Schoot RA, van de Wetering MD, Stijnen T, Tissing WJ, Michiels E, Abbink FC, Raphael MF, Heij HA, Zwaan M, Lieverst JA, Caron HN, van Ommen H; DCOG-Aristocaths Supportive Care Working Group. Prevalence of symptomatic and asymptomatic thrombosis in pediatric oncology patients with tunneled central venous catheters. *Pediatr Blood Cancer* 2016; **63**: 1438–44.

12 Mahajerin A, Petty JK, Hanson SJ, Thompson AJ, O'Brien SH, Streck CJ, Petrillo TM, Faustino EV. 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. *J Trauma Acute Care Surg* 2017; **82**: 627–36.

13 Atchison CM, Arlikar S, Amankwah E, Ayala I, Barrett L, Branchford BR, Streiff M, Takemoto C, Goldenberg NA. Development of a new risk score for hospital-associated venous thromboembolism in noncritically ill children: findings from a large single-institutional case-control study. *J Pediatr* 2014; **165**: 793–8.

14 Arlikar SJ, Atchison CM, Amankwah EK, Ayala IA, Barrett LA, Branchford BR, Streiff MB, Takemoto CM, Goldenberg NA. Development of a new risk score for hospital-associated venous thromboembolism in critically-ill children not undergoing cardiothoracic surgery. *Thromb Res* 2015; **136**: 717–22.

15 Atchison CM, Amankwah E, Wilhelm J, Arlikar S, Branchford B, Stock A, Streiff M, Takemoto C, Ayala I, Everett A, Stapleton G, Jacobs ML, Jacobs JP, Goldenberg NA. Risk factors for hospital-associated venous thromboembolism in critically-ill children following cardiothoracic surgery or therapeutic cardiac catheterization. *Cardiol Young* 2017. [In Press].

16 Amankwah EK, Atchison CM, Arlikar S, Ayala I, Barrett L, Branchford BR, Streiff M, Takemoto C, Goldenberg NA. Risk factors for hospital-sssociated venous thromboembolism in the neonatal intensive care unit. *Thromb Res* 2014; **134**: 305–9.

17 Meier KA, Clark E, Tarango C, Chima RS, Shaughnessy E. Venous thromboembolism in hospitalized adolescents: an approach to risk assessment and prophylaxis. *Hosp Pediatr* 2015; **5**: 44–51.

18 Tolbert J, Carpenter SL. Common acquired causes of thrombosis in children. *Curr Probl Pediatr Adolesc Health Care* 2013; **43**: 169–77.

19 Branchford BR, Gibson E, Manco-Johnson MJ, Goldenberg NA. Sensitivity of discharge diagnosis ICD-9 codes for pediatric venous thromboembolism is greater than specificity, but still suboptimal for surveillance and clinical research. *Thromb Res* 2012; **129**: 662–3.

20 Asfaw AB, Punzalan RC, Yan K, Hoffmann RG, Hanson SJ. Screening Guidelines for Venous Thromboembolism Risk in Hospitalized Children Have Low Sensitivity for Central Venous Catheter-Associated Thrombosis. *Hosp Pediatr* 2017; **7**: 39–45.

21 Dittmar M, Smith N, Warren B, Clark B, Wathen B, Hammett K, Reiter P, Hilden J, Goldenberg N, Branchford B. Improved sensitivity and specificity of pediatric hospital-acquired venous thromboembolism case identification by addition of radiographic and pharmacologic elements. *Thromb Res* 2017; **154**: 93–5.

22 Chalmers EA. Epidemiology of venous thromboembolism in neonates and children. *Thromb Res* 2006; **118**: 3–12.

23 Van Arendonk KJ, Schneider EB, Haider AH, Colombani PM, Stewart FD, Haut ER. Venous thromboembolism after trauma: when do children become adults? *JAMA Surg* 2013; **148**: 1123–30.

24 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–4.

25 Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, Vesely SK. 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* 2012; **141**: e737S–801S.

26 Badawy SM, Rychlik K, Sharathkumar AA. Current practice of pharmacological thromboprophylaxis for prevention of venous thromboembolism in hospitalized Children: a survey of pediatric hemostasis and thrombosis experts in North America. *J Pediatr Hematol Oncol* 2016; **38**: 301–7.

27 Lyle CA, Sidonio RF, Goldenberg NA. New developments in pediatric venous thromboembolism and anticoagulation, including the target-specific oral anticoagulants. *Curr Opin Pediatr* 2015; **27**: 18–25.

28 Meister B, Kropshofer G, Klein-Franke A, Strasak AM, Hager J, Streif W. Comparison of low-molecular-weight heparin and antithrombin versus antithrombin alone for the prevention of symptomatic venous thromboembolism in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2008; **50**: 298–303.

29 Hanson SJ, Faustino EV, Mahajerin A, O'Brien SH, Streck CJ, Thompson AJ, Petrillo TM, Petty JK. Recommendations for venous thromboembolism prophylaxis in pediatric trauma patients: a national, multidisciplinary consensus study. *J Trauma Acute Care Surg* 2016; **80**: 695–701.

30 Guzman D, Sabharwal S, Zhao C, Sabharwal S. Venous thromboembolism among pediatric orthopedic trauma patients: a database analysis. *J Pediatr Orthop B* 2017. https://doi.org/10.1097/BPB.0000000000000424. [Epub ahead of print]

31 Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, Veale K, Rodriquez L, Hopkins RO. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007; **35**: 139–45.

32 Quigley SM, Curley MA. Skin integrity in the pediatric population: preventing and managing pressure ulcers. *J Soc Pediatr Nurs* 1996; **1**: 7–18.

33 Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. *Br J Haematol* 2007; **138**: 430–45.

34 Palmer C. Major trauma and the injury severity score–where should we set the bar? *Annu Proc Assoc Adv Automot Med* 2007; **51**: 13–29.