20th VASCULAR SOCIETY OF EGYPT
INTERNATIONAL ANNUAL CONFERENCE

In Collaboration With

7th ANNUAL AL-AZHAR VASCULAR
SURGERY CONFERENCE

EVIDENCE BASED
VASCULAR PRACTICE

Evidence based management of DVT in children

Dr Eslam Barsim MD,MRCS

Menofia University, Egypt

Q1) What is the difference between adult and pediatric thrombosis ?

- Neonates and children differ from adults in physiology, pharmacologic responses to drugs, epidemiology, and long-term consequences of thrombosis.
- Differences in the physiology of the coagulation system before puberty are reflected in the lower prevalence of VTE in children when compared with adults.
- Vitamin K-dependent clotting factors are circulating at only 50% of adult concentrations at birth and the concentration of alpha-2-macroglobulin (an important inhibitor of thrombin) is typically double that found in adults.

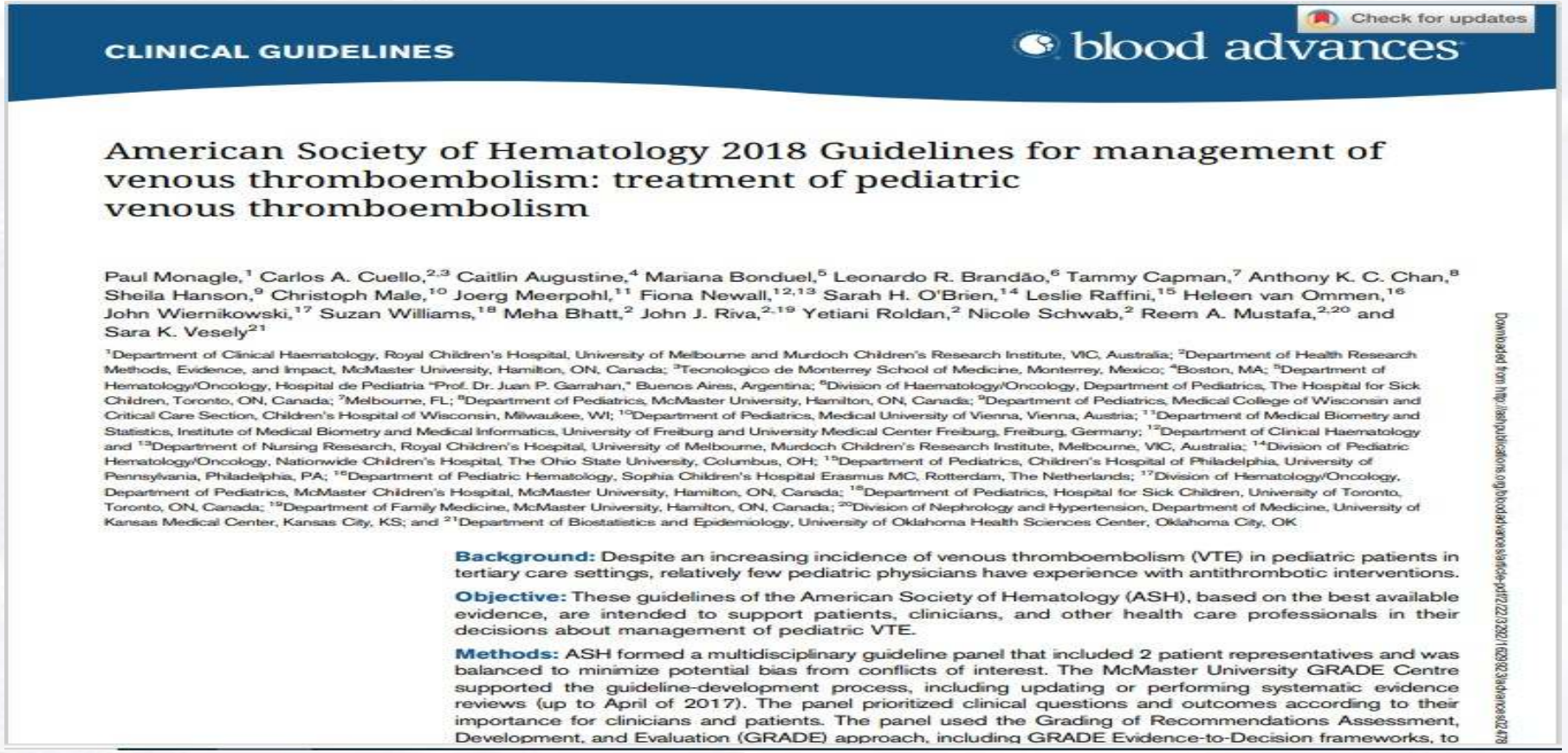
- National registry data suggest an incidence of 5-8 cases of symptomatic VTE per 10 000 hospital admissions (0.05%-0.08%).
- The true incidence could be significantly higher as the majority of VTEs are clinically silent.
- More than 80% of pediatric VTE events occur in children with 1 or more risk factors.
- There are 2 peaks in the incidence of VTE, 1 in infants less than 2 years old and the other at adolescence.

Q2) Are there clinical reference for prevention and treatment of VTE in children ?

- There is a paucity of evidence-based data on the prevention and treatment of VTE in pediatric patients.
- Most guidelines is based on medical data or clinical experience derived from adult patients.
- We performed a quality assessment and comparison of clinical practice guidelines (CPGs) for the prevention and treatment of venous thromboembolism (VTE) in pediatric patients.

- About six clinical practice guidelines are included.

ASH 2018 American Society of Hematology.



CLINICAL GUIDELINES

blood advances

Check for updates

American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

Paul Monagle,[1] Carlos A. Cuello,[2,3] Caitlin Augustine,[4] Mariana Bonduel,[5] Leonardo R. Brandão,[6] Tammy Capman,[7] Anthony K. C. Chan,[8] Sheila Hanson,[9] Christoph Male,[10] Joerg Meerpohl,[11] Fiona Newall,[12,13] Sarah H. O'Brien,[14] Leslie Raffini,[15] Heleen van Ommen,[16] John Wiernikowski,[17] Suzan Williams,[18] Meha Bhatt,[2] John J. Riva,[2,19] Yetiani Roldan,[2] Nicole Schwab,[2] Reem A. Mustafa,[2,20] and Sara K. Vesely[21]

[1]Department of Clinical Haematology, Royal Children's Hospital, University of Melbourne and Murdoch Children's Research Institute, VIC, Australia; [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [3]Tecnologico de Monterrey School of Medicine, Monterrey, Mexico; [4]Boston, MA; [5]Department of Hematology/Oncology, Hospital de Pediatria "Prof. Dr. Juan P. Garrahan," Buenos Aires, Argentina; [6]Division of Haematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada; [7]Melbourne, FL; [8]Department of Pediatrics, McMaster University, Hamilton, ON, Canada; [9]Department of Pediatrics, Medical College of Wisconsin and Critical Care Section, Children's Hospital of Wisconsin, Milwaukee, WI; [10]Department of Pediatrics, Medical University of Vienna, Vienna, Austria; [11]Department of Medical Biometry and Statistics, Institute of Medical Biometry and Medical Informatics, University of Freiburg and University Medical Center Freiburg, Freiburg, Germany; [12]Department of Clinical Haematology and [13]Department of Nursing Research, Royal Children's Hospital, University of Melbourne, Murdoch Children's Research Institute, Melbourne, VIC, Australia; [14]Division of Pediatric Hematology/Oncology, Nationwide Children's Hospital, The Ohio State University, Columbus, OH; [15]Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA; [16]Department of Pediatric Hematology, Sophia Children's Hospital Erasmus MC, Rotterdam, The Netherlands; [17]Division of Hematology/Oncology, Department of Pediatrics, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada; [18]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [19]Department of Family Medicine, McMaster University, Hamilton, ON, Canada; [20]Division of Nephrology and Hypertension, Department of Medicine, University of Kansas Medical Center, Kansas City, KS; and [21]Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Despite an increasing incidence of venous thromboembolism (VTE) in pediatric patients in tertiary care settings, relatively few pediatric physicians have experience with antithrombotic interventions.

Objective: These guidelines of the American Society of Hematology (ASH), based on the best available evidence, are intended to support patients, clinicians, and other health care professionals in their decisions about management of pediatric VTE.

Methods: ASH formed a multidisciplinary guideline panel that included 2 patient representatives and was balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including updating or performing systematic evidence reviews (up to April of 2017). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to

(APAGBI) Association of Pediatric Anesthetists of Great Britain and Ireland guideline 2018

Accepted: 15 February 2018
DOI: 10.1111/pan.13355

SPECIAL INTEREST ARTICLE

WILEY Pediatric Anesthesia

Prevention of perioperative venous thromboembolism in pediatric patients: Guidelines from the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI)

Judith Morgan[1] | Matthew Checketts[2] | Amaia Arana[3] | Elizabeth Chalmers[4] | Jamie Maclean[5] | Mark Powis[6] | Neil Morton[7] | On behalf of the Association of Paediatric Anaesthetists of Great Britain and Ireland Guidelines Working Group on Thromboprophylaxis in Children

[1]Department of Anaesthesia, Sheffield Children's Hospital, Sheffield, UK
[2]Department of Anaesthesia, NHS Tayside, Dundee, UK
[3]Department of Anaesthesia, Leeds Teaching Hospital, Leeds, UK

Summary
The Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) Guidelines Working Group on Thromboprophylaxis in Children has reviewed the literature and where possible provided advice on the care of children in the periopera-

ACCP 2012 American College of Chest Physicians.

CHEST Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy in Neonates and Children

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Paul Monagle, MBBS, MD, FCCP; Anthony K. C. Chan, MBBS; Neil A. Goldenberg, MD, PhD; Rebecca N. Ichord, MD; Janna M. Journeycake, MD, MSCS; Ulrike Nowak-Göttl, MD; and Sara K. Vesely, PhD

Background: Neonates and children differ from adults in physiology, pharmacologic responses to drugs, epidemiology, and long-term consequences of thrombosis. This guideline addresses optimal strategies for the management of thrombosis in neonates and children.
Methods: The methods of this guideline follow those described in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.
Results: We suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism (Grade 2C). When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist (Grade 2C). We suggest that therapeutic unfractionated heparin in children is titrated to achieve a target anti-Xa range of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C). For neonates and children receiving either daily or bid therapeutic low-molecular-weight heparin, we suggest that the drug be monitored to a target range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous injection or, alternatively, 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C).

EAST 2016 Eastern Association for the Surgery of Trauma.

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

Arash Mahajerin, MD, MSCr, John K. Petty, MD, Sheila J. Hanson, MD, MS, A. Jill Thompson, PharmD, Sarah H. O'Brien, MD, Christian J. Streck, MD, Toni M. Petrillo, MD, *and* **E. Vincent S. Faustino, MD, MHS**, *Orange, California*

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.

LEVEL OF EVIDENCE: Systematic review/meta-analysis, level III.
KEY WORDS: Deep vein thrombosis; injury severity score; intensive care; pediatric; wounds and injuries.

Poland 2021 Guidelines on the prevention and treatment of venous thromboembolism in cancer patients treated surgically including patients under 18 years of age

China 2021 Guidelines for the selection and pharmacological monitoring of anticoagulant drugs for the prevention and treatment of VTE

Chinese Journal of Clinical Pharmacology , 2021, 37 (21) Peking University Core CSCD

2021 Guidelines for the selection and pharmacological monitoring of anticoagulant drugs for the prevention and treatment of venous thromboembolism in China

Wang Qiaoyu Wu Mingfen Liu Xin Wang Xiaoyan Chen Yaolong Zhao Zhigang

Department of Pharmacy, Beijing Tiantan Hospital, Capital Medical University , Medical Department, Beijing Tiantan Hospital, Capital Medical University , and Center for Evidence-Based Medicine, School of Basic Medical Sciences, Lanzhou University

Summary: Venous thromboembolism has attracted more and more attention from the medical community in recent years. These guidelines are developed in accordance with the World Health Organization (WHO) guidelines for the development of guidelines, and the evaluation of evidence and recommendations is graded by the Rating, Development and Evaluation of Assessment Recommendations (GRADE). In order to better guide the clinical practice of physicians and pharmacists in China, this guideline systematically evaluates the evidence-based evidence in the use of anticoagulant drugs in the prevention and treatment of deep vein thrombosis, and gives recommendations from the perspective of pharmacists for a total of 30 clinical problems such as the selection of anticoagulant drugs, pharmaceutical monitoring, and the treatment of anticoagulant drug overdose in different departments, so as to further standardize the rational use of anticoagulant drugs in the prevention and treatment of venous thromboembolism in China.

Keyword: venous thromboembolism; deep vein thrombosis; anticoagulant medications; pharmacy monitoring; Guide;

DOI: 10.13699/j.cnki.1001-6821.2021.21.032

Album: Medicine and health science and technology

Risk factors of VTE in pediatric patients

- Three guidelines described the risk factors of VTE in children.

- The APAGBI 2017 guideline highlighted that the risk factors of VTE in children include an age < 1 or >13 years, a central venous access devices (CVAD), surgical history, malignancy, infection/sepsis, major trauma, drugs, immobility, pregnancy, congenital thrombophilia, acquired thrombophilia, obesity (BMI > 30 kg/m2), cardiac disease, inflammatory bowel disease, and sickle cell disease.

- The EAST 2016 guideline highlighted that the risk factors of VTE in children also include mechanical ventilation and the use of recombinant factor VIIa.

- The Poland 2021 guideline highlighted that the risk factors of VTE in children with cancer also included chemotherapy, anticancer treatment, and the type, location, and stage of cancer.

Prevention of VTE in pediatric patients

- Five guidelines made recommendations for the prevention of VTE in pediatric patients.
- The prevention methods for VTE include basic prophylaxis, mechanical prophylaxis, and pharmacological prophylaxis.
- Although the contents of the recommendations achieved consensus in most areas, there were some noteworthy differences in the guidelines.
- Basic prophylaxis for VTE was recommended; this prophylactic measure entailed ensuring adequate fluid intake, moving early, and avoiding prolonged periods of immobility.

- Pharmacological prophylaxis was recommended for children aged ≥13 years with multiple thrombotic risk factors but no bleeding risk in both China 2021 and APAGBI 2017 guidelines.
- For mechanical prophylaxis, both China 2021 and APAGBI 2017 guidelines recommended the use of mechanical methods including intermittent pneumatic compression devices and anti-embolism stockings for at-risk children aged ≥13 years, to reduce VTE risk.
- EAST 2016 guideline recommended considering mechanical prophylaxis for children hospitalized after trauma (aged ≥15 years, and in younger, post-pubertal children with an injury severity score of >25).

Prevention of VTE in specific high-risk situations :

- Two guidelines made recommendations for patients with cancer: both China 2021and Poland 2021 guidelines recommended pharmacologic antithrombotic prophylaxis for all children undergoing major surgery with a history of cancer-related or unrelated DVT, if not contraindicated; additionally, low molecular weight heparin (LMWH) was recommended.

- For the prevention of VTE in patients requiring cardiac catheterization via an artery, the China 2021 guideline recommended the administration of unfractionated heparin (UFH) or aspirin as thromboprophylaxis;

- however, the ACCP 2012 guideline recommended the administration of UFH as thromboprophylaxis over no prophylaxis or aspirin, as previous studies have demonstrated that prophylactic anticoagulation with UFH reduced the incidence of femoral artery thrombosis from 40 % to 8 % in patients after cardiac catheterization, whereas the use of aspirin did not significantly reduce the incidence of femoral artery thrombosis.

Treatment of VTE in pediatric patients

- Four guidelines made recommendations regarding the treatment of VTE in pediatric patients.
- These included thrombectomy, thrombolytic therapy, antithrombin replacement therapy, and anticoagulation therapy, of which anticoagulation was the main treatment method.
- The anticoagulant drugs recommended in the guidelines for the treatment of VTE in children included LMWH, UFH, VKAs, and direct oral anticoagulants (DOACs); however, recommendations varied between guidelines.

Treatment of VTE	China 2021	Poland 2021	ASH 2018	ACCP 2012
Thrombectomy	–	In children with CAT, targeted thrombolysis or thrombectomy can be considered, based on an individual benefit-risk assessment.	In pediatric patients with symptomatic DVT or PE, suggests against using thrombectomy or IVC filter followed by anticoagulation; rather anticoagulation alone should be used.	Thrombectomy followed by anticoagulation is recommended for pediatric patients with life-threatening VTE, and placement of a retrievable IVC filter is recommended if anticoagulation is contraindicated.

Treatment of VTE	China 2021	Poland 2021	ASH 2018	ACCP 2012
Thrombolytic therapy	-	In children with CAT, targeted thrombolysis or thrombectomy can be considered, based on an individual benefit-risk assessment.	In pediatric patients with symptomatic DVT or PE, suggested against using thrombolysis followed by anticoagulation, but for pediatric patients with hemodynamically unstable PE, thrombolysis followed by anticoagulation was recommended.	Thrombolytic therapy was recommended only for life-threatening or limb-threatening thrombosis and was not recommended for neonates.
Anti thrombin replacement	-	-	Suggests using AT replacement therapy in addition to standard anticoagulation in pediatric patients with DVT/CSVT/PE who have failed to respond clinically to standard anticoagulation treatment and reveals low AT levels based on age appropriate reference ranges.	-

Treatment of VTE	China 2021	Poland 2021	ASH 2018	ACCP 2012
Anticoagulation therapy	Anticoagulation therapy was recommended for children with VTE.	For children with CAT to prevent recurrence of VTE, anticoagulant is recommended for the treatment of VTE.	In pediatric patients with symptomatic DVT or PE, anticoagulation was recommended; in pediatric patients with asymptomatic DVT or PE, suggests either using anticoagulation or no anticoagulation.	In children with first VTE, acute anticoagulant therapy with either UFH or LMWH was recommended.
Anticoagulant drugs	For children with VTE,recommended to use VKA, heparin or rivaroxaban.	LMWHs or UFHs are routinely recommended in children with cancer and acute VTE. DOACs is recommended if at low risk of bleeding and in the absence of drug interaction.	In pediatric patients with symptomatic DVT or PE, suggests using either LMWH or VKAs.	The anticoagulant drugs recommended in this guideline include UFH, LMWH, and VKAs.

Treatment of VTE	China 2021	Poland 2021	ASH 2018	ACCP 2012
Anticoagulant duration	-	For the treatment course of cancer patients, LMWH or DOACs should be used for at least 6 months.	In pediatric patients with provoked DVT or PE suggests using anticoagulation for ≤3 months, while with unprovoked DVT or PE suggests using anticoagulation for 6 to 12 months.	In children with secondary VTE in whom the risk factor has resolved, suggest anticoagulant therapy for 3 months; in children who have ongoing but potentially reversible risk factors, suggest continuing anticoagulant therapy beyond 3 months; in children with idiopathic VTE, suggest anticoagulant therapy for 6 to 12 months.

Summary and Conclusion

- VTE in pediatric patients has different characteristics from that in adults. Additionally, there is a paucity of evidence-based data on the prevention and treatment of VTE in pediatric patients and a considerable portion of the available evidence cited in the guidelines is based on medical data or clinical experience derived from adult patients.
- Traditional anticoagulants (heparin and VKA) remain the standard of care in the management of VTE in pediatric patients; however, DOACs for the treatment of VTE in children have shown efficacy and safety results similar to those in adults.

- Thus, a significant change in the status of DOACs recommendations in guidelines for the treatment of VTE in children can be expected in the future. Moreover, recommendations should be periodically revised as new evidence emerges and multiple factors must be considered at the clinical level, rather than relying solely on the routine application of guidelines.

Thank you