Plan to Revise the 2018 ASH Clinical Practice Guidelines on Pediatric VTE

Background and Rationale

The ASH guidelines on treatment of pediatric venous thromboembolism (VTE) were published in 2018 (Monagle et al. 2018). In 2022, an ASH librarian refreshed the original literature searches, and the results were reviewed by 3 experts who authored the 2018 guidelines (Drs. Paul Monagle, Christophe Male, and Leslie Raffini). On the recommendation of these experts, the ASH Committee on Quality agreed on July 21, 2022, to revise the guidelines.

New data supporting revision include randomized clinical trials of direct oral anticoagulants (DOACs) in children that have resulted in their licensure and use in clinical practice (Palumbro et al. 2022; Sanchez et al. 2022; Connor et al. 2020; Thom et al. 2020; Young et al. 2020; Male et al. 2020; Lensing et al. 2018; Kubitza et al. 2018; Brandao et al. 2020; Halton et al. 2021) and a randomized clinical trial evaluating the duration of anticoagulation for provoked VTE (Goldenberg et al. 2021). These studies provide a higher level of evidence to guide pediatric VTE and have changed the current treatment landscape. New observational studies also provide evidence relevant to recommendations from the 2018 guidelines (Jaffray et al. 2022; Pelland-Marcotte et al. 2019; Ross et al. 2022; Belsky et al. 2020; Ortel et al. 2020), and additional trials are expected, e.g., SAXOPHONE (Payne et al. 2022) and PREVAPIX-ALL (O’Brien et al. 2022).

Because of this new evidence, many aspects of the 2018 guidelines are now outdated, including statements “No anticoagulants are approved for use in children” and “DOACS should only be used within the context of formal clinical trials.” Importantly, the recommendations requiring revision are those with the highest impact, including: 1) which anticoagulant(s) to use for VTE, in part, based on location and inclusion in the DOAC trials; 2) duration of anticoagulation for provoked VTE; 3) management of asymptomatic catheter-related VTE; 4) management of submassive pulmonary embolism; and 5) when to remove a catheter in the setting of VTE and pulmonary embolism.

The 2018 guidelines recommend low molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs) for treatment of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) (recommendation 13) and give additional guidance for the treatment of VTE specific to symptoms and/or location. With the introduction of the DOACs, there is now evidence to support use of DOACs for VTE specific to some symptoms or location (DVT, PE, cerebral sinovenous thrombosis [CSVT]) but not others (renal vein thrombosis [RVT] or portal vein thrombosis [PVT]).

In the new trials, DOACs were used under very specific conditions (only after a parenteral agent for >5 days, requirement for consistent oral intake, and exclusion of patients on certain drugs, or with renal or liver impairment). Furthermore, very few neonates or infants were included in the studies. Through new recommendations, remarks, and discussion about the design and limitations of the new studies, ASH guidelines are expected to help clinicians use DOACs appropriately in children.
Scope

In this revision effort, a single guideline panel will address 10 clinical questions, including 7 questions from the 2018 guidelines and 3 new questions about prevention of pediatric VTE. If feasible, >10 questions may be addressed. To determine feasibility, the guideline panel will collaborate with a methodology team to define additional questions. The methodology team will then perform scoping reviews to understand level of effort required to systematically search for and synthesize available evidence. The ASH Committee on Quality will review and approve any proposed additional work.

The 7 questions from the 2018 guidelines to be revised include the following:

Anticoagulation in symptomatic and asymptomatic DVT or PE
The systematic reviews informing recommendations 1 and 2 from the 2018 guidelines will be updated to include the new DOAC trials. Data from the new trials is expected to improve certainty in estimates of the effects of anticoagulation. Estimates in the 2018 guidelines are based on observational studies and extrapolations from adult data.

LMWH vs. VKAs
Recommendation 13 from the 2018 guidelines, addressing choice of anticoagulant, will be reevaluated and revised to compare DOACs vs LMWH vs VKAs.

Anticoagulation in subpopulations
Four recommendations address anticoagulation in subpopulations with specific thrombosis, i.e., patients with right atrial thrombosis (17), neonates with RVT (recommendation 19), patients with PVT (recommendation 21), and patients with CSVT (22a, 22b). These recommendations are based on observational studies. Randomized trials are not yet available. However, new observational studies may better inform these recommendations. The systematic reviews will therefore be updated, and depending on what is found, these recommendations may be revised.

New recommendations that recommend in favor of DOACs will include remarks or discussion about optimal implementation, including the following:

- Timing of commencement
- Stability of oral feeding
- Role of monitoring
- Thresholds of organ dysfunction
- Use of concomitant drugs
- Interruptions for procedures
- Platelet thresholds
- Suitability of preparations for younger age groups
- Reversal strategies

These remarks or discussion will not be based on a systematic review of evidence. Similar information may also be provided for unfractionated heparin, LMWH, and VKAs.

New recommendations will also be developed to address 3 questions about prevention of pediatric VTE. The following are example questions. Through a brainstorming and prioritization process, the guideline
panel will prioritize the questions. More than 3 questions may be practical if the same evidence review informs multiple questions. The methodology team will advise the guideline panel and ASH:

1. In children with leukaemia and CVAD, should anticoagulant prophylaxis be given over no prophylaxis?
2. In children with solid cancers and CVAD, should anticoagulant prophylaxis be given over no prophylaxis?
3. In children with home TPN and CVAD should anticoagulant prophylaxis be given over no prophylaxis?
4. In children with short term CVAD (NICU/PICU) should anticoagulant prophylaxis be given over no prophylaxis?
5. In children with congenital or acquired heart disease who require long term thromboprophylaxis should we use LMWH vs VKAs vs DOACS vs antiplatelets?
6. In children with anticardiolipin antibodies/lupus, should anticoagulant prophylaxis be given over no prophylaxis?
7. Do hospitalized children require anticoagulation prophylaxis versus no prophylaxis?
8. Do children admitted to intensive care require thromboprophylaxis over no thromboprophylaxis?
9. Do neonates admitted to intensive care require thromboprophylaxis over no thromboprophylaxis?

The new guideline panel will review outcomes previously prioritized. However, no changes are expected. Updating of the original systematic reviews will therefore exclude quality assessment and data extraction from previously included studies.

Other questions from the 2018 guidelines
The following are out of scope for this revision effort, unless (1) prioritized by the guideline panel, (2) determined by the methodology team to be practical to address in addition to the 10 questions described above, and (3) approved by the ASH Committee on Quality:

Seven recommendations from the 2018 guidelines address the use of interventions in addition to or instead of anticoagulation, i.e., thrombolysis (recommendations 3, 4, 5, 20), thromboectomy (6), inferior vena cava (IVC) filter (7), and antithrombin replacement therapy (8). New evidence from observational studies could change these recommendations. If for practical or other reasons, the systematic reviews informing the old recommendations are not updated, discussion in the guideline report may provide new context for the old recommendations.

Three recommendations around purpura fulminans (24, 25, 26) will be out of scope for this effort. This rare disorder has been recently addressed by a guidance from the International Society of Thrombosis and Hemostasis (ISTH ref). The ISTH guidance will be referenced.

Perspective
These guidelines will provide recommendations for high-resource settings internationally, taking an individual patient perspective (i.e., rather than the perspective of a health system or of policymakers). It is expected that the recommendations may need to be adapted for other settings or perspectives.
Good Practice Statements

Good practice statements are strong recommendations that are not based on a systematic review of evidence and are formed outside of the evidence-to-decision process used to develop graded recommendations for ASH guidelines. The 2018 guidelines include one good practice statement. New such statements may be included in the revised guidelines, provided they meet criteria defined by GRADE (Izcovich et al. 2020, Guyatt et al. 2016).

Panel Composition

ASH will form a single guideline panel of about 25 individuals. The panel will mainly include experts in pediatric hematology. Other clinical specialties represented on the panel will include pediatric nursing with a specialization in anticoagulation (1 panelist), cardiology (1 panelist), neonatal and pediatric intensive care (1 panelist), and pharmacology (1 panelist). The panel will also include patient representatives, i.e., individuals with lived experience of the disease, such as a past patient or a caregiver. At least 1 panelist will be an early career hematologist. At least 1 panelist will represent the perspective of a pediatric hematologist who practices in a typical community setting (i.e., not a major research academic setting).

The panel will be diverse with respect to intellectual point of view on the guideline questions, geography, and demographics. Consistent with the goal of developing recommendations for high-resource settings, panelists will be considered from north and south America, Europe, and Asia pacific regions.

Individuals with methodological expertise may be included on the panel, or this expertise may be provided by the methodology team that supports the panel under a paid agreement with ASH.

A member of the ASH Guideline Oversight Subcommittee will serve on the guideline panel as an ex officio member. This individual’s role will be to ensure that the guideline development process is conducted in accordance with this project plan and ASH policies and procedures, including ensuring that questions are within scope, reviewing participant disclosures and ensuring adherence to ASH COI policies, and critically reviewing the guideline report for publication.

An early career member of the guideline panel will be asked to serve in a “writer” role. Responsibilities of this role will include drafting background clinical content, recording panel decisions and discussion points, drafting the guideline report, integrating edits by authors into the guideline report, and addressing comments receiving during public review. At the beginning of the project, panel leadership will discuss and agree with the writer how to appropriately recognize his or her contributions on publication.

Organizational Collaborators

ASH will not invite other organizations to collaborate in the funding, development, or approval of these guidelines. However, ASH may invite other organizations to recommend experts for the guideline panel, if experts are needed from outside the ASH membership, and to review and endorse the guidelines. ASH will also explore with other relevant organizations opportunities to promote and disseminate the guidelines. In addition to endorsement, this could include announcements, summaries, commentaries, or educational programs about the guidelines. Relevant other organizations for which such
opportunities will be explored include the American Society of Pediatric Hematology/Oncology (ASPHO) and ISTH.

**Methodology Team**

Under a paid agreement with ASH, a methodology team will support the guideline development process, including conducting systematic reviews of available evidence.

**Methods**

The ASH guideline development process includes the following steps:

1. ASH forms a guideline panel.
2. The panel prioritizes guideline questions.
3. The methodology team in collaboration with experts on the guideline panel systematically reviews available evidence.
4. The guideline panel reviews and finalizes evidence summaries and forms recommendations.
5. ASH makes the recommendations available for public comment.
6. The guideline panel and the methodology team write a report of the guidelines for publication and dissemination.
7. ASH committees and officers review and approve publication of the guidelines under the imprimatur of ASH.
8. Authors submit the guidelines report to *Blood Advances* for review and publication.

The GRADE approach will be used to assess certainty of evidence (Guyatt et al. 2008). The GRADE Evidence-to-Decision framework (Alonso-Coello et al. 2016) will be used to make judgments about the available evidence and form guideline recommendations using standardized language that has well-defined interpretations for clinicians, patients, and policymakers (Izcovich et al. 2020).

Systematic reviews will be conducted according to standards defined by the Cochrane Collaboration or equivalent. Specific methods used will depend upon the nature and quality of the best available evidence.

For each guideline question, the best available evidence will be used to make estimates about the health effects of alternative interventions. These estimates, in combination with other judgments, will support recommendations by the guideline panels. As described above under Background and Scope, new randomized controlled trials are available for some of the planned guideline questions. This evidence will be systematically identified, appraised, and used. For other questions, randomized trials are not expected. In this case, evidence from other study designs (e.g., nonrandomized studies or indirect comparisons from studies of alternative interventions against placebo) will be systematically collected, appraised, and used, or if the guideline panel agrees, evidence from studies in other populations (i.e., indirect evidence) may be used. Pragmatic methods may be used to identify indirect evidence.

The scope of this effort includes questions for which published evidence is known to be available. If questions are later prioritized for which no published studies can be found to make estimates, the guideline panel may choose not to answer the question with a recommendation. Alternatively, the panel may base recommendations on the systematically collected clinical experiences of experts. These clinical
Experiences may be collected and synthesized from available registries or from surveys, including convenience surveys of the experts serving on the guideline panel, as was done for the 2018 guidelines (Mustafa et al. 2021).

Initial panel meetings will be held virtually via Zoom. In-person meetings could occur in 2023, if the COVID-19 pandemic allows, and if considered necessary. If not, the development process will be conducted virtually using online tools including the GRADEPro Guideline Development Tool, including to summarize evidence, obtain panel voting, and document panel judgments and decisions.

Management of Conflicts of Interest
Conflicts of interest of all participants will be managed in accordance with general ASH policies, as described on the ASH website (https://www.hematology.org/about/governance/conflict-of-interest), and with specific ASH policies and procedures determined by the ASH Guideline Oversight Subcommittee. The most recent version of these policies is attached as Appendix A.

Publication Strategy
Publication strategy for the guidelines and any other intellectual property will be determined by ASH, including the ASH Guideline Oversight Subcommittee. As described in Appendix X, the current strategy is to submit and publish all work relating to this project including the guideline reports and systematic reviews within ASH’s online-only open access scientific journal, Blood Advances. At the beginning of the project, a presubmission inquiry to the editors of Blood Advances will describe all planned work. The inquiry and discussions with the editors will be led by the lead authors and by the GOS ex officio member(s) of the panels.

One guideline report is expected.

Systematic reviews may be developed for submission to Blood Advances as separate, simultaneous publications. If the reviews are not prepared as separate publications, details about the reviews will be included with the guideline reports as supplements.

Authorship, sponsorship, and acknowledgements of such publications will be in accordance with academic standards and customs and requirements of the journal of publication. ASH authorship criteria for the guidelines are presented as Appendix B.

Dissemination and Implementation
To support understanding and implementation of the guidelines, the panel will be asked to write recommendations and remarks that are clear and actionable.

The chair and panelists will strategize a dissemination and implementation plan that will enhance access, for clinicians and patients, to the guideline and support understanding and implementation of the guidelines recommendations. While a formal strategy will be written around the time of public comment, panelists will also be asked to flag recommendations in development for which there are implementation barriers (e.g., insufficient clinician awareness or education, lacking information systems support).
Revision

After publication, ASH will maintain these guidelines through regular revision. The need for revision will be determined through a process that includes annual monitoring for new evidence, expert review, and committee decision-making. When ASH agrees to undertake a revision, a new guideline panel or panels will be appointed, which may include members of the original panel. The new panel will prioritize new and old questions, then follow other usual steps of the ASH guideline development process.
References


