ASH ISTH Draft Recommendations for Anticoagulant Prophylaxis of Pediatric Patients at Risk of Venous Thromboembolism (VTE)

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

<u>These draft recommendations are not final and therefore are not intended for use or citation.</u>

To submit comments on the draft recommendations, **please email guidelines@hematology.org**. Only comments submitted via email will be reviewed by the guideline panel.

The public comment period for these draft recommendations ends **June 12th, 2025**.

RECOMMENDATIONS

LEUKEMIA/LYMPHOBLASTIC LYMPHOMA

- Question 1: *In pediatric patients with leukemia/lymphoblastic lymphoma should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?*
  - **Recommendation 1**: In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests either*** anticoagulant prophylaxis ***or*** no anticoagulant prophylaxis, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).
    - **Remarks:**
      - The panel noted that the pooled evidence suggested a benefit of reduced thrombosis with anticoagulant prophylaxis; however, the panel recognized that prophylactic anticoagulation did not offer benefits for all populations of pediatric patients with leukemia/lymphoblastic lymphoma based on their differing risks. Based on the published literature, populations that may benefit from anticoagulant prophylaxis include those ≥10 years of age or with obesity, T-cell immunophenotype, high-risk acute lymphoblastic leukemia, or personal or family history of thrombosis. Factors that may increase the risk of bleeding with anticoagulant prophylaxis include younger age, prior bleeding, severe thrombocytopenia, and renal dysfunction.
      - The evidence included studies that investigated the effect of anticoagulant prophylaxis during induction and consolidation phases of treatment in Acute Lymphoblastic Leukemia/Lymphoma when the use of asparaginase is virtually

universal. The available evidence implicates asparaginase as an important pro-thrombotic agent. If initiated, the panel suggests anticoagulant prophylaxis be given during asparaginase containing cycles only and discontinued after the prothrombotic effects of asparaginase are anticipated to have reversed.
        - Anticoagulant prophylaxis should be paused peri-procedurally (e.g., lumbar punctures) and dose modified or held during periods of moderate to severe thrombocytopenia, as described below, to reduce the risk of bleeding.
    - Evidence Profile
    - Evidence to Decision Framework

- Question 2: *In pediatric patients with leukemia/lymphoblastic lymphoma should antithrombin supplementation vs no antithrombin supplementation be used?*
    - **Recommendation 2:** In pediatric patients with leukemia/lymphoblastic lymphoma, the ASH ISTH Guideline Panel ***suggests no*** antithrombin supplementation rather than antithrombin supplementation (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).
        - **Remarks**:
            - Evidence from randomized controlled trials suggested a clinically significant benefit of antithrombin supplementation to prevent venous thromboembolism with a small to negligible bleeding risk. However, in one randomized controlled trial, the event free survival was reduced in patients receiving antithrombin supplementation compared to patients receiving unfractionated heparin or low molecular weight heparin.
            - The panel placed a high value on preventing cancer recurrence, therefore suggested no antithrombin supplementation.
            - The panel acknowledged that there is important uncertainty regarding the association between antithrombin and reduced event free survival.
    - Evidence Profile
    - Evidence to Decision Framework

Solid Tumors

- Question 3: *In pediatric patients with solid tumors, including Hodgkin lymphoma, should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used?*
    - **Recommendation 3:** In pediatric patients with solid tumors, including Hodgkin lymphoma, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).
        - **Remarks:**
            - The panel noted that a significant proportion of reported thrombotic events were present at diagnosis and therefore not preventable with prophylactic anticoagulation.
            - The panel considered that there are sub-groups in whom the risk:benefit profile might be in favor of prophylactic anticoagulation, and might include pediatric patients meeting one or more of the following criteria: adolescent cancer patients, oral contraceptive use, vessel compression or invasion by tumor, major cancer surgery, central venous access device utilization, reduced mobility, known

thrombophilia, and/or past history of thromboembolic disease, and without a significant risk of bleeding.

- Evidence Profile
- Evidence to Decision Framework

TPN Prophylaxis

- Question 4: *In infants, children and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
  - **Recommendation 4:** In infants, children, and adolescents considered for total parenteral nutrition (TPN) for more than 60 days (i.e., intestinal failure on home TPN), the ASH ISTH Guideline Panel ***suggests*** using anticoagulant prophylaxis rather than no anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
    - **Remarks**:
      - This recommendation excludes neonates and patients requiring short-term (<60 days) TPN support.
      - Based on the two comparative studies, primary pharmacological prophylaxis seemed to reduce the risk of developing catheter-related VTE.
      - The anticoagulant prophylaxis administered included daily LMWH and vitamin K antagonists.
      - Patients receiving primary and secondary anticoagulant prophylaxis could not be separated in the included studies and thus the evidence includes pediatric patients receiving secondary prophylaxis.
  - Evidence Profile
  - Evidence to Decision Framework

Central Venous Access Device (CVAD)

- Question 5: *In pediatric patients with a short-term (<7 days) CVAD, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
  - **Recommendation 5:** In pediatric patients with a short-term (<7 days) CVAD, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
    - **Remarks:**
      - The current evidence does not support the universal use of prophylactic anticoagulation for all pediatric patients with a short-term (≤7 days) CVAD. However, the panel acknowledges that there may be subgroups of patients at high-risk of VTE and low risk of bleeding, in whom anticoagulant prophylaxis may be of benefit. This high-risk VTE subgroup includes patients with a short-term CVAD who are critically ill, on invasive mechanical ventilation, expected to have prolonged immobility and/or hospitalization, those with autoimmune/inflammatory conditions, and those with active serious infections.
  - Evidence Profile 1
  - Evidence Profile 2
  - Evidence to Decision Framework

- Question 6: *In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or total parental nutrition (TPN) should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
  - **Recommendation 6:** In children and adolescents who require medium/long term (≥8 days) CVAD in the absence of cancer or TPN, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
    - **Remarks:**
      - This recommendation pertains to the use of primary anticoagulant prophylaxis.
      - The panel acknowledged that there may be pediatric patients who may benefit from prophylaxis. A thorough assessment of individual risks and careful consideration of benefits and harms when considering prophylactic anticoagulation is appropriate.
  - Evidence Profile
  - Evidence to Decision Framework

Antiphospholipid Antibodies

- Question 7: *In pediatric patients with antiphospholipid antibody syndrome should secondary anticoagulant (± antiplatelet) prophylaxis vs. no secondary anticoagulant prophylaxis be used?*
  - **Recommendation 7:** In pediatric patients with antiphospholipid antibody syndrome, the ASH ISTH Guideline Panel ***suggests using*** secondary anticoagulant prophylaxis rather than no secondary anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).
    - **Remarks:**
      - An a-priori decision was made to exclude pediatric patients receiving only antiplatelet therapy from this evidence profile.
      - The included evidence showed moderate benefit of secondary anticoagulation prophylaxis (with or without antiplatelet therapy) in reducing recurrent thromboembolism.
  - Evidence Profile
  - Evidence to Decision Framework

- Question 8: *In pediatric patients with persistent antiphospholipid antibodies and without history of thrombosis should primary anticoagulant prophylaxis vs. no primary anticoagulant prophylaxis be used?*
  - **Recommendation 8:** In pediatric patients with persistently positive antiphospholipid antibodies without a history of thrombosis, the ASH ISTH Guideline Panel ***suggests no*** primary anticoagulant prophylaxis rather than primary anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
    - **Remarks:**
      - An a-priori decision was made to exclude pediatric patients receiving antiplatelet therapy, and therefore the panel cannot comment on risk/benefit of using antiplatelet agents in this cohort.
      - The panel acknowledges that evolving definitions of antiphospholipid syndrome may influence clinical decision making and emphasizes that individual patient characteristics—such as the presence of an underlying autoimmune disorder, double

or triple antibody positivity, the strength of antibody titers, and microvascular manifestations should be considered when evaluating the need for primary anticoagulant prophylaxis.

- Evidence Profile
- Evidence to Decision Framework

Trauma Patients

- Question 9: *In pediatric patients with trauma, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
- **Recommendation 9:** In pediatric patients with trauma, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
  - **Remarks:**
    - The evidence does not support the universal use of anticoagulant prophylaxis in pediatric trauma patients who comprise a heterogenous population in whom the overall prevalence of VTE is low.
    - There are, however, subgroups in the included studies (patients deemed "high risk") that had higher reported rates of VTE who may benefit from prophylactic anticoagulation. These specific "high risk" criteria included presence of shock, age > 12 years (or younger ages with multiple risk factors), immobility, intubation, and presence of a CVAD.
    - While the risk for bleeding from anticoagulant prophylaxis in pediatric trauma patients is overall low, it was noted to be higher in patients receiving prophylactic anticoagulation in one study.
- Evidence Profile
- Evidence to Decision Framework

Hospitalized Patients

- Question 10: *In hospitalized pediatric patients, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
  - **Recommendation 10:** In hospitalized pediatric patients, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).
    - **Remarks:**
      - Hospitalized pediatric patients encompass an extremely heterogeneous population with respect to age, underlying medical conditions and baseline risk of thrombosis.
      - The panel acknowledged that there may be certain pediatric patients that may benefit from anticoagulant prophylaxis, though additional studies are needed. Several subgroups (cancer, CVAD, surgery, trauma) are addressed in separate recommendations.
  - Evidence Profile 1
  - Evidence Profile 2
  - Evidence to Decision Framework

Critically Ill Patients

- Question 11: *In pediatric patients who are critically ill with or without a CVAD should primary anticoagulant prophylaxis over no prophylaxis be used?*
  - **Recommendation 11:** In pediatric patients who are critically ill with or without a CVAD, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁⨁◯◯)
    - **Remarks:**
      - The current evidence does not support the universal use of prophylactic anticoagulation in critically ill children for which there is insufficient data for formal stratification of the risks of VTE and the risk of bleeding.
      - However, the panel acknowledged that there may be subsets of critically ill children (children ≥1 year old with an untunneled CVAD and low risk of bleeding and children receiving invasive mechanical ventilation), in whom the risk of VTE may outweigh the risk of bleeding, who could potentially benefit from prophylactic anticoagulation.
  - Evidence Profile 1
  - Evidence Profile 2
  - Evidence to Decision Framework

Surgery Patients

- Question 12: *In pediatric patients undergoing noncardiac surgery, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?*
  - **Recommendation 12:** In children undergoing noncardiac surgery, the ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
    - **Remarks:**
      - The panel did not assess VTE risk by specific type of surgical procedure (e.g., orthopedic, bariatric, laparoscopic, etc.). Rather, the panel grouped available pediatric surgical data to assess the risk for postoperative VTE and found a low incidence in this heterogeneous group.
      - Procedure-related and patient-related factors that increase the risk for VTE include longer operative time, prolonged immobilization, greater than 7 days of central venous access, obesity, congenital thrombophilia, and the use of combined oral contraceptives.
  - Evidence Profile
  - Evidence to Decision Framework