Prophylaxis for Pediatric Patients at Risk of Venous Thromboembolism (VTE)

An Educational Slide Set

2026 American Society of Hematology International Society of Thrombosis and Haemostasis guidelines for prophylaxis for pediatric patients at risk of venous thromboembolism

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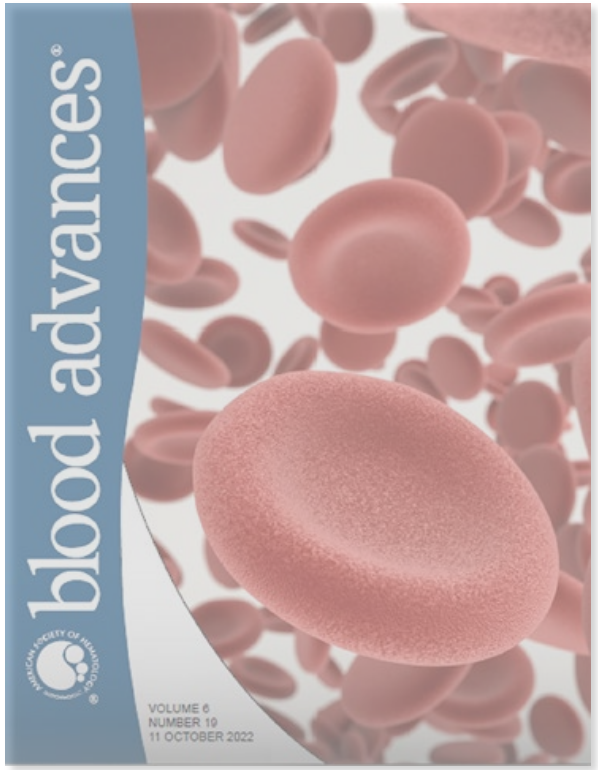

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ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. Prevention and Treatment of VTE in Patients with Cancer
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. **Prevention and Treatment of Pediatric VTE**
9. VTE in the Context of Pregnancy
10. Diagnosis of VTE

How were these guidelines created?

PANEL FORMATION

Guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology)
- Patient representative
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

10 clinically-relevant questions generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question

"In pediatric patients with a short-term (≤7 days) CVAD, should anticoagulant prophylaxis vs. no anticoagulant prophylaxis be used?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

	STRONG Recommendation		CONDITIONAL Recommendation	
	"The panel recommends…"	"The panel recommends against…"	"The panel suggests…"	"The panel suggests against…"
				
For patients	Most individuals would want the intervention.		A majority would want the intervention, but many would not.	
For clinicians	Most individuals should receive the intervention.		Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.	

Objectives

By the end of this session, you should be able to

1. Describe recommendations for prophylaxis in children with acute leukemia/lymphoblastic lymphoma (ALL/LL)
2. Describe recommendations for prophylaxis in children receiving long-term home total parenteral nutrition (TPN)
3. Describe recommendations for prophylaxis in critically ill children
4. Describe recommendations for prophylaxis in children with antiphospholipid antibody syndrome (APS)

Pediatric VTE prophylaxis strategies should be risk-stratified and subgroup specific

VTE is a significant complication among **hospitalized children** and those with **chronic medical conditions**

VTE in children has a complex pathophysiology with different pediatric subgroups exhibiting **distinct thrombosis and bleeding risk profiles**.

Anticoagulant prophylaxis strategies for VTE prevention in children need to be age stratified and cannot simply be extrapolated from adult strategies

Development of **risk-stratified** and **subgroup-specific** anticoagulant prophylaxis strategies is critical for the prevention of pediatric VTE

Good Practice Statement 1

- In pediatric patients at increased risk for VTE, the decision regarding the use of anticoagulant prophylaxis ***requires careful consideration of not just the patient's individual*** **risk for thrombosis** but, importantly, their **risk of bleeding**
- Using the principle of **"first do no harm"**, anticoagulant prophylaxis should not be initiated in those considered to be at high risk of major or clinically relevant non-major bleeding even if the perceived risk of VTE is high
- The benefit:risk ratio for the use of anticoagulant prophylaxis for VTE prevention in each patient should be reassessed regularly

Good Practice Statement 2

- In pediatric patients receiving anticoagulant prophylaxis, decisions regarding the peri-procedural interruption of anticoagulation, including timing and duration, should be made by carefully balancing the individual patient's risk of bleeding and thrombosis complications, as well as the specific risks associated with the procedure
- Institutions are encouraged to develop **guidelines for the optimal management of peri-procedural anticoagulant prophylaxis**, especially around lumbar puncture or spinal anesthetic procedures for which the potential complications of bleeding are significant

Case 1: Anticoagulant prophylaxis in a child with ALL

- A 13-year-old boy is admitted to pediatric floor with:
  - WBC count of 80,000 per microliter
  - Hemoglobin 6 g/dl
  - Platelet count 25,000 per microliter
- A diagnosis of T cell – ALL is made
- After receiving packed red cell and platelet transfusions, a lumbar puncture (LP) is performed and a central venous access device (CVAD) is placed to start chemotherapy
- The patient is started on induction chemotherapy with vincristine, daunorubicin, prednisone and cal-asparaginase
- There is no family history of VTE

Case 1: Anticoagulant prophylaxis in a child with ALL

Question 1: The oncologist is concerned about risk of thrombosis and inquires about starting anticoagulant prophylaxis. What recommendation would you give at this point?

A. Start anticoagulation and continue during the duration of treatment

B. Start anticoagulation and continue during asparaginase containing cycles only

C. Do not start anticoagulation

Both are reasonable options based on risk and patient preference

Recommendation

- The ASH ISTH Guideline Panel ***suggests either*** anticoagulant prophylaxis ***or*** no anticoagulant prophylaxis for patients with leukemia / lymphoblastic lymphoma, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences

The evidence was based on two randomized control trials (RCTs) and three non-RCTs

The two RCTs evaluated effects of enoxaparin (THROMBOTEC) and apixaban (PREVAPIX-ALL) on the development of VTE

Anticoagulation prophylaxis appeared to reduce risk of all VTE but the estimate was imprecise and there was a median risk of 1% of major bleeding, which was not different than standard of care

*Goldenberg N, et al; *JAMA*, 2022

Further Considerations

- The patient population is too heterogenous with regard to both VTE and bleeding risk to make a general recommendation for or against anticoagulant prophylaxis
- Several patient populations appear to benefit from anticoagulant prophylaxis and have more to gain from its use:
  - Those with obesity
  - ≥10 years old
  - T-Cell immunophenotype
  - High or very high risk ALL
  - Prior thrombosis or a family history of thrombosis

Further Considerations

- Common factors that increase the risk of thrombosis in patients with hematological malignancies include:
  - Asparaginase therapy
  - Presence of a CVAD
- If initiated, pharmacological anticoagulant prophylaxis should be given exclusively during **asparaginase-containing cycles** of chemotherapy

Case 1: Anticoagulant prophylaxis in a child with ALL

- After careful consideration decision is made to start anticoagulation with apixaban.
  - Hold for platelet counts below 30×10^9 per µl
  - Interrupt at least 48 hours prior to procedures (e.g.; LP) and resume no sooner than 18–24 hours after
- The oncology team inquires about antithrombin (AT) replacement due to concerns with asparaginase use depleting AT levels and contributing to thrombosis risk
- How would you advise?

A. Check AT level and replace if the level is low

B. Replace AT prophylactically to prevent thrombosis

C. Do not recommend replacing AT prophylactically

Recommendation

The ASH ISTH Guideline Panel ***suggests against*** antithrombin supplementation in pediatric patients with leukemia/lymphoblastic lymphoma

The panel noted a clinically significant benefit of AT supplementation to prevent VTE and symptomatic VTE

The risk of bleeding was small following AT supplementation

However, there was possible reduced event-free survival (EFS) in children receiving AT supplementation

The balance of effects probably favored avoiding the use of AT supplementation

Case 1: Conclusion

- Patient with T-ALL finished all asparaginase containing phases of chemotherapy on apixaban without any evidence of VTE
- Discontinuation of anticoagulation at this time is appropriate
- He continues to do well on maintenance chemotherapy without anticoagulant prophylaxis

Case 1: Summary

Guidelines ***suggest*** consider ***either*** anticoagulant prophylaxis **or** none for patients with leukemia / lymphoblastic lymphoma, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences

If initiated, anticoagulant prophylaxis should be given exclusively during asparaginase-containing cycles of chemotherapy

Guidelines ***suggests against*** AT supplementation in pediatric patients with leukemia/lymphoblastic lymphoma mainly due to possible reduced EFS in children receiving AT supplementation

Case 2: Anticoagulant prophylaxis in a child requiring long-term TPN

- A 2-month-old infant with short gut syndrome and ileal atresia had a Broviac CVAD placed for long-term TPN
- The infant is tolerating very small amounts of enteral feeds but is reliant on TPN for their nutritional requirements
- There is no previous history of VTE
- The plan is to discharge the infant on home TPN, with daily hospital in the home support

Case 2: Anticoagulant prophylaxis in a child requiring long-term TPN

Question 1: The gastroenterologist is concerned about risk of thrombosis and inquires about starting prophylactic anticoagulation

What recommendation would you give at this point?

A. Start anticoagulation and continue for the duration of CVAD
B. Start anticoagulation if there are signs of CVAD dysfunction
C. Do not start anticoagulation

Recommendation

- In pediatric patients (infants, children and adolescents) considered for TPN for more than 60 days (i.e., intestinal failure on home PN), the ASH ISTH Guideline Panel ***suggests*** using primary anticoagulant prophylaxis

Based on two comparative non-randomized studies, primary anticoagulant prophylaxis seemed to reduce the risk of developing CVAD-related VTE

This recommendation excludes neonates and patients requiring short-term (<60 days) TPN support

Patients receiving primary and secondary anticoagulant prophylaxis could not be separated thus the evidence includes pediatric patients receiving secondary anticoagulant prophylaxis

The anticoagulant prophylaxis administered included daily low molecular weight heparin (LMWH) and vitamin K antagonists (VKAs)

Case 2: Anticoagulant prophylaxis in a child requiring long-term TPN

- The inclusion of patients receiving secondary prophylaxis, selection bias, the small number of events, the small number patients included in the studies and hence the imprecision of the estimates affects the certainty of the evidence → ***Conditional recommendation***
- Based on the two non-randomized comparative studies, primary anticoagulant prophylaxis seemed to reduce the risk of developing CVAD-related VTE (RR: 0.83, 95% CI: 0.23 to 2.98)
  - Propensity score stratification was used in one study[1] to balance the effects of covariates that were significantly different between the anticoagulant prophylaxis and non-prophylaxis groups. Primary anticoagulant prophylaxis reduced the risk of CVAD-related VTE (OR: 0.64, 95% CI: 0.12 to 3.40)

1. Demirok et al. Prophylactic anticoagulation in children receiving home parenteral nutrition: An international prospective multicenter study." Clinical Nutrition. 2025. **46**: 88-95.

Case 2: Anticoagulant prophylaxis in a child requiring long-term TPN

Immediately after the Broviac was inserted, prophylactic anticoagulation was started with LMWH

Question 2: Which anticoagulant would you recommend for the ongoing management of this patient?

A. Continue LMWH
B. Transition the patient to a VKA
C. Transition the patient to a direct oral anticoagulant (DOAC)

Case 2: Anticoagulation prophylaxis in a child requiring long-term TPN

Immediately after the Broviac was inserted, prophylactic anticoagulation was started with LMWH

Question 2: Which anticoagulant would you recommend for the ongoing management of this patient?

A. Continue LMWH

B. Transition the patient to VKA

C. Transition the patient to a DOAC

Both are reasonable options

No studies report the use of DOACs in infants or children on long-term TPN

Case 2: Conclusion

- After two months on LMWH, the infant was transitioned to a VKA
- Remained on a VKA long-term
- Nil episodes of major bleeding or thrombosis
- Target INR 2.5 therapeutic range of 2.0- 3.0
- Supported to monitor the INR at home

Case 2 Summary

Given the need for lifelong vascular access for most children on home TPN, and the life-threatening consequences of loss of vascular access, the panel placed a high value on potential benefits of anticoagulant prophylaxis.

Due to the small number of bleeding events reported only in two studies, the risk of adverse effects was not estimable.

Case 3: Anticoagulant prophylaxis in a child critically ill

- A 4-year-old toddler is admitted to the pediatric ICU with influenza and respiratory failure
- There is no personal or family history of VTE
- The patient is intubated and a left femoral CVAD is placed

Case 3: Anticoagulant prophylaxis in a child critically ill

Question 1: The ICU calls for recommendations on VTE prophylaxis due to the child's critically ill status and presence of CVAD

What would you recommend?

A. Start anticoagulation prophylaxis with LMWH until child is extubated and then discontinue

B. Start anticoagulation prophylaxis with a DOAC until child is extubated and then discontinue

C. Do not start anticoagulation prophylaxis since the child has a short-term illness

D. Place mechanical thromboprophylaxis until child is extubated

Recommendation

The ASH ISTH guideline panel ***suggests*** no anticoagulation prophylaxis rather than anticoagulant prophylaxis

- The guidelines do not address the use of mechanical thromboprophylaxis, including intermittent pneumatic compression devices

Six studies informed this recommendation:
- *One RCT
- Five non-randomized studies of intervention (NRSI)

One RCT and ****two** prospective cohort studies assessed primary anticoagulant prophylaxis in critically ill children with CVADs

*****One** case-control study evaluated anticoagulant prophylaxis in critically ill children on invasive mechanical ventilation

*Faustino EV et al, Crit Care Med 2021;**Jones et al, Blood 2019; Quinn et al, J Thromb Haemost 2024; ***Sochet et al, Pediatr Crit Care Med 2024

Case 3: Anticoagulant prophylaxis in a child critically ill

- The *CRETE RCT study reported a reduced risk of developing a CVAD-related VTE (both symptomatic and clinically unsuspected) in critically ill children who received anticoagulant prophylaxis (RR: 0.56, 95% CI: 0.27 to 1.15)
  - A greater reduction in risk was observed when the analysis was limited to symptomatic CVAD-related VTE (RR: 0.13; 95% CI: 0.02 to 0.96)
- Noteworthy points:
  - Only 2.5% of all screened patients with a CVAD were ultimately randomized
  - Nearly 60% of screened patients were deemed ineligible due to a high risk of bleeding, which was defined by factors such as active or recent clinically relevant bleeding, recent surgery or major trauma, coagulopathy, or renal failure
  - Four of the 27 children randomized to receive enoxaparin did not receive the intervention, further limiting the internal validity of the trial

*Faustino EV et al, Crit Care Med 2021

Case 3: Anticoagulant prophylaxis in a child critically ill

The certainty of evidence for benefits, harms, and burden was considered low due to serious imprecision → **Conditional recommendation**

- 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, and who could potentially benefit from prophylactic anticoagulation

Case 3: Conclusion

- The patient recovered from influenza infection, was extubated and his CVAD removed in less than one week
- Given the resolution of VTE provoking factors, no anticoagulation prophylaxis at this time is appropriate
- He did not develop any signs or symptoms of VTE during his hospitalization and remains well

Case 3: Summary

The panel does not suggest universal use of anticoagulant prophylaxis in all critically ill children

Certain subgroups of critically ill children, particularly those at high risk of VTE but at low risk of bleeding, might still benefit from individualized consideration of anticoagulation prophylaxis

Case 4: Anticoagulant prophylaxis in a child with antiphospholipid antibodies (APLA)

- 14-year-old previously well adolescent presents with 4-week history of abdominal pain, headaches, dizziness, fatigue and 2-day history of hematuria
- Anemia and thrombocytopenia on bloodwork, proteinuria on urinalysis
- Investigated for systemic erythematous lupus (SLE)
- Identified to have positive APLA

Case 4: Anticoagulant prophylaxis in a child with APLA

This adolescent has positive APLA without thrombosis

Should anticoagulant prophylaxis be offered?

A. Initiate anticoagulation with UFH
B. Initiate anticoagulation with LMWH
C. Initiate anticoagulation with a DOAC
D. Do not initiate anticoagulation

Case 4: Anticoagulant prophylaxis in a child with persistent APLA

The patient is seen in follow-up 3 months later and continues to have APLA identified

This adolescent has persistent positive APLA without a history of thrombosis

Should anticoagulant prophylaxis be offered?

A. Initiate anticoagulation with VKA
B. Initiate anticoagulation with LMWH
C. Initiate anticoagulation with a DOAC
D. Do not initiate anticoagulation

Recommendation 8

- The ASH ISTH guideline panel ***suggests no*** primary anticoagulant prophylaxis rather than primary anticoagulant prophylaxis in pediatric patients with persistently positive antiphospholipid antibodies without a history of thrombosis

Notes:

- A-priori decision was made to exclude patients receiving antiplatelet therapy
- Evolving definitions of antiphospholipid syndrome (APS) may influence clinical decision making
- Individual patient characteristics should be considered:
  - Underlying autoimmune disorder, double or triple antibody positivity, antibody titers, microvascular manifestations, other thrombophilia

Zero studies from systematic review

One adult RCT comparing low dose ASA to ASA + warfarin

Expert evidence survey of panel members

Recommendation 8

Adult open-label RCT comparing low-dose aspirin to low-dose aspirin plus low-intensity warfarin in adult patients with positive APLA

- No difference in VTE incidence
- Higher rate of bleeding events in patients receiving anticoagulant prophylaxis

Recommendation 8

Expert evidence approach via survey of panel members

- Targeted questions to estimate number of patients managed by each expert and rates of thrombosis and bleeding
- 16 responses; 88 children with persistently positive APLA without thrombosis

Outcomes	Primary Anticoagulant Prophylaxis (n=5)	No Primary Anticoagulant Prophylaxis (n=83)
Symptomatic VTE	1/5 (20%)	2/83 (2%)
Major bleeding	0	0
CRNM	1/5 (20%)	0/83 (0%)

Recommendation 8

The certainty of evidence for benefits, harms, and burden was considered very low based due to risk of recall and perception bias

→ ***Conditional recommendation***

The panel recognized that

- Expert survey did not address high risk VTE periods
    - Hospitalization, prolonged immobility, infection, CVAD presence
- Thrombotic risk and bleeding risk should be balanced

Case 4: Anticoagulant prophylaxis in a child with APS

- One month later (4 months from original diagnosis):
  - Presents with 4-day history of right leg pain and swelling
  - SLE flare
- Doppler ultrasound: occlusive thrombus from popliteal to common femoral vein
- Anticoagulant therapy initiated

Case 4: Anticoagulant prophylaxis in a child with APS

- On follow-up at 3 months post-VTE diagnosis
  - SLE disease activity improved
  - Residual non-occlusive thrombosis on doppler ultrasound
  - APLA continues to be positive

Case 4: Anticoagulant prophylaxis in child with APS

This adolescent has completed 3 months of anticoagulation for provoked VTE in the setting of underlying SLE disease activity which has now improved, but APLAs are persistently positive

How would you manage patient at this point?

A. Discontinue anticoagulation, as patient has completed 3 months of treatment

B. Transition to long-term anticoagulant prophylaxis for secondary VTE prevention

C. Continue anticoagulant at treatment dose until thrombus resolves completely on US

D. Switch to aspirin

Recommendation 7

The ASH ISTH Guideline Panel ***suggests*** using secondary anticoagulant prophylaxis rather than no secondary anticoagulant prophylaxis in pediatric patients with antiphospholipid antibody syndrome

Notes:

- *A-priori* decision was made to exclude patients receiving antiplatelet therapy
- Included evidence showed moderate benefit of secondary anticoagulation prophylaxis (with or without antiplatelet therapy) in reducing recurrent thromboembolism

Three NRSI studies **Two** single centre observational study **One** cross sectional international database study	**One** subgroup analysis RCT	**Expert evidence survey** of panel members

Rao AAN et al. Blood Coagulation & Fibrinolysis, April 2017. Avcin T et al. Pediatrics. 2008. Brandão LR et al. Blood Adv. 2022. Ma J et al. Clin Rheumatol. 2018.

Recommendation 7

- Patients who received antiplatelet agents only (e.g. aspirin and clopidogrel) excluded
- Rate of recurrent thrombosis in children with APS 21.3%
- Anticoagulant prophylaxis associated with reduction in risk of recurrent events
- Studies did not provide data on the rate of bleeding
- Only subgroup analysis of the phase 2B/3 DIVERSITY trial reported bleeding as an outcome
    - No bleeding events reported in children with APS treated with Dabigatran
- Data from subgroup analysis of DIVERSITY trial and panel survey led to undesirable effects of anticoagulation being deemed trivial

Children with APS treated with secondary anticoagulant (+/- antiplatelet prophylaxis)

Outcomes	Number of patients		Effect	
	Secondary Anticoagulant (+/- antiplatelet prophylaxis)	No secondary anticoagulant prophylaxis	Relative (95% CI)	Absolute (95% CI)
Thrombus recurrence	23/133 (17.3 %)	11/25 (44%)	**RR: 0.41** (0.23 to 0.76)	**250 fewer per 1000** (339 to 106 fewer)
Bleeding	4/517	0/1 (0.0%)		

Panel Survey: 13 responses, N=157

- major bleeding events in 2 (1.27%) patients
- CRNM bleeding events in 12 (7.6%) patients

Case 4: Conclusion

- Patient initially had persistent APLA positivity and no thrombosis – not managed with primary anticoagulant prophylaxis
- Then had a provoked VTE in the setting of underlying SLE disease activity on a background of persistent APLA positivity
- VTE treated and anticoagulation transitioned to long-term secondary prophylaxis given continued presence of APLA positivity

Case 4: Summary

DOACs not recommended in adult patients with APS, specifically triple-positive APS, history of arterial thrombosis
Similar data not available for pediatric patients, but LMWH and VKA extrapolated to be anticoagulants of choice

Burden of treatment likely significant, given use of injectable drugs (LMWH), food and drug interactions (VKA), need for laboratory monitoring (LMWH and VKA), extended duration anticoagulation in children with APS

Case 4: Summary

Future areas of study include prospective studies investigating:

- Risk stratification strategies and prognostic impact of primary anticoagulant prophylaxis in pediatric patients with persistently positive APLA and no history of thrombosis, at baseline and during periods of high VTE risk
- Natural history of APS in children
  - Risk of recurrent thrombosis in children with single versus double and triple positive APLA
- Safety and efficacy of different types of anticoagulant agents (LMWH, VKA and DOACs) in children with low-risk APS
- Magnitude of undesirable effects of anticoagulation in children with APS, including bleeding and reduced QoL

Other guideline recommendations that were not covered in this session

For these topics, conditional recommendations were made based on low or very low certainty of evidence

- Prophylaxis in patients with solid tumors including Hodgkin's Lymphoma
- Prophylaxis in patients (excluding oncology and TPN) with short term (≤7 days) and medium to long-term (≥8 days) CVAD
- Prophylaxis in patients with trauma
- Prophylaxis in hospitalized patients
- Prophylaxis in non-cardiac surgical patients

Future Priorities for Research

- Development, validation and refinement of risk assessment models of pediatric VTE to help identify those children at high risk of VTE and low risk of bleeding
- High-quality evidence investigating the safety and efficacy of anticoagulant prophylaxis for VTE prevention across different pediatric subgroups
- Evaluation of the optimal prophylactic dosing, timing and duration of different anticoagulant agents, including DOACs, across various clinical scenarios and pediatric subgroups

In Summary: Back to our Objectives

1. **Describe recommendations for prophylaxis in children with acute lymphoblastic leukemia**
   - The ASH ISTH guideline panel ***suggests either*** anticoagulant prophylaxis or no anticoagulant prophylaxis for patients with leukemia / lymphoblastic lymphoma, based on the individual assessment for risk of thrombosis and bleeding and patients' values and preferences.
   - The Panel also ***suggests no*** AT supplementation for patients with leukemia / lymphoblastic lymphoma.
2. **Describe recommendations for the prophylaxis in children receiving long term home total parenteral nutrition**

   The ASH/ ISTH Guideline Panel ***suggests*** using primary pharmacological prophylaxis.

In Summary: Back to our Objectives

3. **Describe recommendations for prophylaxis in critically ill children**

   The ASH ISTH Guideline Panel ***suggests no*** anticoagulant prophylaxis rather than anticoagulant prophylaxis.

4. **Describe recommendations for prophylaxis in children with antiphospholipid antibody syndrome**

   The ASH/ISTH guideline panel ***suggests no*** primary anticoagulant prophylaxis rather than primary anticoagulant prophylaxis in pediatric patients with persistently positive APLA without a history of thrombosis

   The ASH ISTH Guideline Panel ***suggests*** using secondary anticoagulant prophylaxis rather than no secondary anticoagulant prophylaxis in pediatric patients with APS

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See more about the **ASH VTE guidelines** at *hematology.org/VTEguidelines*