Asparaginase-related Venus thromboembolism

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Introduction

- **Asparaginase can induce a hypercoagulable state that may cause catastrophic thrombosis**
- **Mechanism of VTE with asparaginase is multifactorial and involves decreased synthesis of asparagine-containing proteins such as ATprothrombin; factors V, VII, VIII, IX, X, XI; fibrinogen; protein C; protein S; von Willebrand factor (VWF); and plasminogen**

prevalence

- **A meta-analysis of 1752 children in 17 studies of ALL/LBL reported that 5 percent of patients had a thromboembolic event during treatment (83 percent occurred during induction therapy)**
- **27-41%in adults**
- **Symptomatic thrombosis :1.8 percent of patients, but rose to 15 percent in children with prothrombotic risk factors**

Type of asparaginase

- **L-asparaginase produced from *Escherichia coli* *has an* profound effects on coagulation**
- ***Erwinia* asparaginase is an alternate preparation that may have fewer effects.**
- **In a series of 11 adults with acute lymphoblastic leukemia (ALL) who were treated with *Erwinia* asparaginase, there was significant lowering of antithrombin levels**

RECOMMENDATIONS AND GUIDELINES

The prevention and management of asparaginase-related venous thromboembolism in adults: Guidance from the SSC on Hemostasis and Malignancy of the ISTH

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wileyonlinelibrary.com/journal/jth J Thromb Haemost. 2020;18:278–284.

Thromboprophylaxis in adults with ALL

- **ISTH GUIDLINE suggest infusion of antithrombin concentrate for levels below 50% to 60%.**
- **ISTH GUIDLINE suggest LMWH thromboprophylaxis during induction phase of ALL therapy that includes asparaginase.**

Thromboprophylaxis in children with ALL

- **Two randomized trials in pediatric populations :**
  - **In the PARKAA trial,109 children were randomized in a 1:2 ratio to receive weekly antithrombin infusions according to a repletion formula (N = 37) or no intervention (N = 72). The incidence of asymptomatic VTE in the antithrombin repletion arm was 28%.which was statistically similar to those who did not receive antithrombin infusions 37%.**

Thromboprophylaxis in children with ALL

❖**The second study:**

949 children were randomized to receive enoxaparin, antithrombin alone, or low-dose intravenous unfractionated heparin in a 1:1:1 ratio. Antithrombin was monitored prior to scheduled asparaginase administration and repleted for levels below 80%. The rate of VTE was higher among those randomized to unfractionated heparin (25 of 312, 8%) than in the enoxaparin (11 of 317, 3.5%, *P* = .011) or antithrombin groups (6 of 320,1.9%, *P* < .001). The rates of VTE between enoxaparin and antithrombin were not statistically different.

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A systematic review and meta-analysis of the effectiveness of primary thromboprophylaxis in acute lymphoblastic leukemia during early-phase therapy including asparaginase or its prolonged form

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The PREVAPIX-ALL study(COG-2019)
DOAC?

- **Evaluating the safety and efficacy of weight-adjusted twice daily apixaban—(DOAC)— compared with standard of care (SOC) of no systemic anticoagulant in induction phase.**
- **256 children in each group(total 512 children)**
- **Unfortunately, this large, well conducted trial did not show any benefit of apixaban in reducing the rate of thromboembolism with a similar risk of major bleeds but higher risk of clinically relevant non-major (CRNM) bleeds than SOC, especially in children younger than 10 years.**

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Oral Abstracts

332.Thrombosis and Anticoagulation: Clinical and Epidemiological

Thromboembolism (VTE) in Obese Patients with Newly Diagnosed Pediatric Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma (ALL/LL) a Sub-Study Analysis of the Prevapix-ALL/Children's Oncology Group ACCL1333 Trial-2023

Results:

- **82 obese patients**
- **Obesity was defined as ≥ 95 th percentile for age and sex specific body mass index as per the Centers for Disease Control and Prevention childhood obesity definition.**
- **Forty-two were randomized to apixaban and 40 were randomized to SOC .For the primary efficacy outcome there was a statistically significant decrease in VTE events in the apixaban arm, 1/42 (2.4%) compared to the SOC arm 10/40 (25%) [p 0.0067]**
- **No statistically significant difference was observed in bleeding between the two groups**

Thromboprophylaxis in pediatric ALL/LMWH

- **In a prospective cohort study of 112 children, the combination of enoxaparin (1 mg/ kg/daily) with antithrombin repletion resulted in a lower rate of VTE (0%) compared with those who received antithrombin repletion alone (12.7%) (target, plasma AT levels >50 percent).LMWH combined with antithrombin supplementation might be effective for pediatric patients with ALL.**

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THE LANCET
Haematology

COMMENT · Volume 11, Issue 1, E3-E5, January 2024

Thromboprophylaxis in paediatric acute lymphoblastic leukaemia

Thromboembolism is a serious complication in children with acute lymphoblastic leukaemia, resulting in morbidity, mortality, and adverse leukaemia outcomes.[1–3] Although thromboembolism is largely preventable, use of anticoagulants in children with acute lymphoblastic leukaemia is challenging since both the disease and myelosuppressive chemotherapy increase bleeding risk. Further, low molecular weight heparin (LMWH)—the preferred anticoagulant for children with

participate and 33% in the LMWH group switched to other groups.[5]

The PREVAPIX-ALL study, reported by Sarah H O'Brien and colleagues in *The Lancet Haematology*, tried to circumvent this problem by evaluating the safety and efficacy of weight-adjusted twice daily apixaban—a direct oral anticoagulant (DOAC) inhibiting Factor Xa—compared with standard of care (SOC) of no systemic anticoagulant.[6] Unfortunately, this large, well conducted

Asymptomatic thrombosis

- **In PREVAPIXALL clinically unsuspected (or asymptomatic) CVL related thromboembolisms detected by screening ultrasonography or echocardiogram were 86%.**
- **A prospective cohort study with Doppler ultrasound at three timepoints during induction to evaluate CVL-related thromboembolism showed that the majority of the asymptomatic thromboembolisms were transient and spontaneously resolved**
- **Are patients and physicians willing to accept the added risk of bleeding to prevent an asymptomatatic clot when the clinical significance of the clot is unknown ?**

lancet/haematology .January 2024

Thromboprophylaxis is only indicated for patients at high risk of thrombosis .Who is at high risk of thrombosis?

1. **High-risk acute lymphoblastic leukaemia who receive intensified therapy including a high number of ASPARAGINASE doses (a known culprit in the development of thromboembolism) along with steroids and anthracyclines, which are also implicated in thrombogenesis.**

2. **Children aged 10 years or older are categorized as having high-risk acute lymphoblastic leukaemia and receive high-intensity therapy.**

lancet/haematology .January 2024

Management of VTE in asparaginase therapy
ISTH GUIDLINE

- **We suggest LMWH for the acute management of VTE related to asparaginase therapy if severe thrombocytopenia (platelet count < 50 x 109/L) is anticipated. Following resolution of severe thrombocytopenia, DOAC may be considered in the absence of other relative contraindications such as major drug interactions**

- **For life-threatening VTE such as cerebral venous thrombosis or central PE, we suggest short-term concurrent administration of antithrombin concentrate until therapeutic anticoagulation and clinical stability is established**

Anti-thrombin therapy?

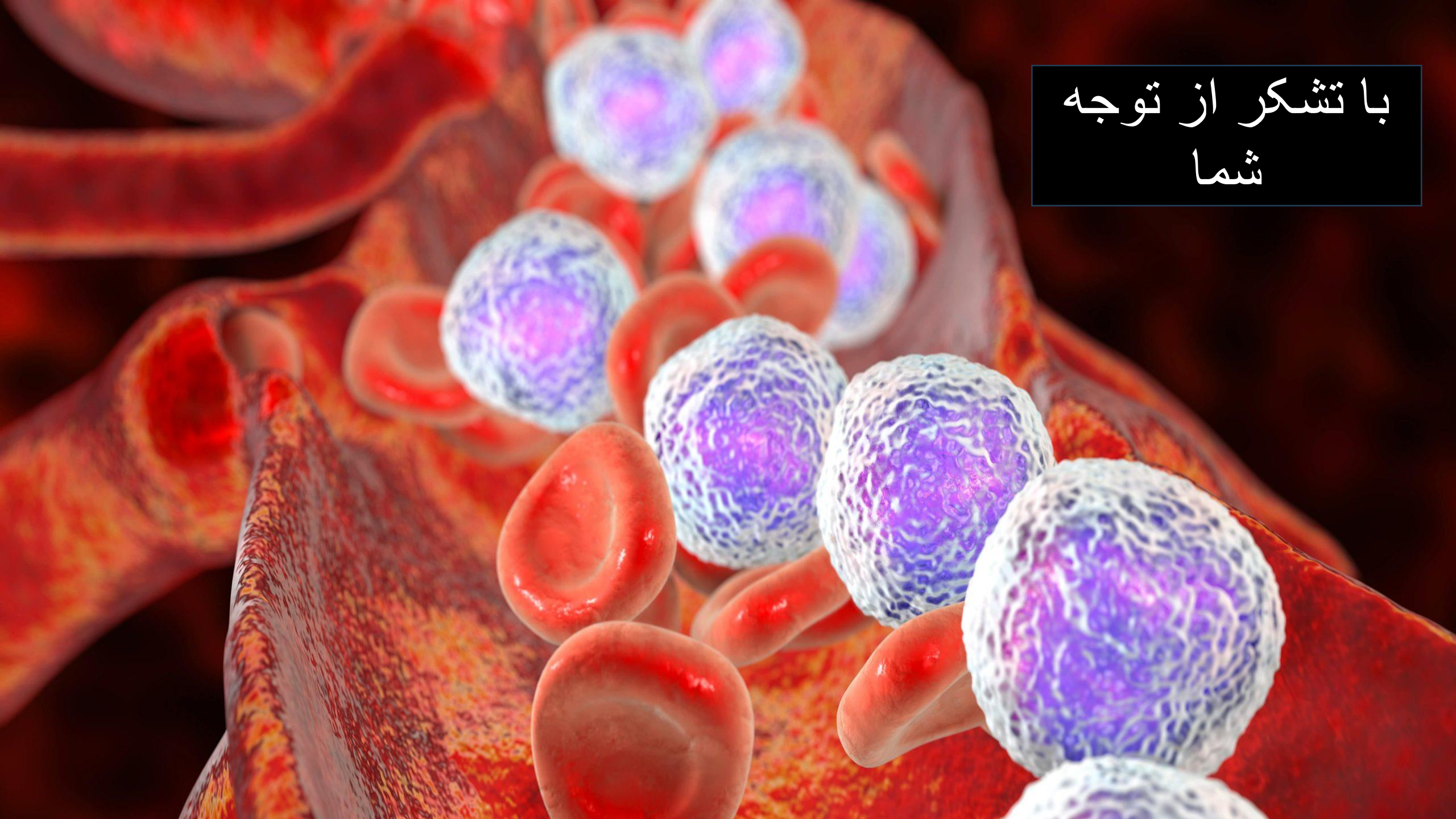
- **Other experts use FFP or Cryoprecipitate as a source of AT, and others use anticoagulation alone (without AT replacement), based on lack of high quality evidence that administering AT improves outcomes**

Holding asparaginase therapy
ISTH GUIDLINE

- **For high-risk thrombotic events such as cerebral venous or sinus thrombosis, central PE, proximal DVT, or arterial thrombosis we recommend holding asparaginase therapy, at least temporarily.**
- **There is limited literature on the safety of resumption of asparaginase following a cerebral venous thrombosis (considered on a case-by-case basis accounting for number of asparaginase doses missed, resolution of thrombosis and symptomatology, and ongoing VTE risk factors,and only under the cover of anticoagulation)**
- **For non high risk thrombotic events We suggest the consideration to resume asparaginase following successful stabilization of the acute thrombotic event (approximately 4 weeks).**

Duration of treatment
ISTH GUIDLINE

- **We recommend at least 6 months of therapeutic anticoagulation for treatment of VTE associated with asparaginase.**
- **In those patients who developed a life-threatening VTE such as cerebral venous thrombosis, central PE, proximal DVT, or arterial thrombosis and are not otherwise considered at increased risk for hemorrhage, we suggest continuation of anticoagulation until completion of chemotherapy and achievement of complete remission.**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