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SHORT REPORT

A survey on thromboprophylaxis and coagulation assessment in children and young adults with acute lymphoblastic leukaemia (ALL) in the Nordic and Baltic countries: Different practices of assessment and management

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Summary

Patients undergoing treatment for acute lymphoblastic leukaemia (ALL) are at risk of coagulopathy, especially thromboembolism. We conducted a survey on practices in the assessment and management of coagulopathy during the new ALLTogether protocol in 29 (17 paediatric, 12 adult) Nordic and Baltic cancer centres. While 92% of adult centres used thromboprophylaxis with low-molecular-weight heparin, no paediatric centre did. Almost all providers performed baseline coagulation studies,

Abbreviations: ALL, acute lymphoblastic leukaemia; DOACs, direct-acting oral anticoagulants; LMWH, low-molecular-weight heparin; LP, lumbar puncture.

but only 59% continued the assessment. Fibrinogen replacement was conducted in 59%, and antithrombin replacement in 28% of the centres. The survey highlights the need for guidelines in the management of coagulopathy during ALL therapy.

KEYWORDS
ALL, antithrombin, childhood leukaemia, paediatric haemostasis, paediatric thrombosis, thrombosis

INTRODUCTION

Thrombosis and pulmonary embolism are well-known complications in acute lymphoblastic leukaemia (ALL), affecting about 6% of all children under 18 years, and up to 20% of adolescents and young adults with ALL.[1,2] T-cell immunophenotype, mediastinal mass, central venous catheters, immobilisation, and infections increase the risk of thrombosis.[3] ALL treatment *per se* is a known risk factor for thrombosis, especially asparaginase and corticosteroids.[4,5] Asparaginase affects several haemostatic proteins, leading to coagulopathies such as low antithrombin and hypofibrinogenaemia.[6,7] Thromboprophylaxis in ALL patients has been discussed over the years. Beside antithrombotic agents such as low-molecular-weight heparin (LMWH) and in later years direct-acting oral anticoagulants (DOACs), replacement of antithrombin has even been used. In addition to thromboembolic events, patients are at risk of bleeding.[8] Thrombocytopenia is usually well controlled, but patients with ALL can develop disseminated intravascular coagulation, hepatic insufficiency or hypofibrinogenaemia.

In the Nordic and Baltic countries, patients with ALL aged 1–45 years have been treated according to the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocols until 2019. The NOPHO group treats circa 230 patients with ALL aged 1–45 years per year, the majority (ca 190) 1–18 years old. Now, a European treatment protocol, ALLTogether (A2G) was implemented, with participating study groups from the five Nordic countries, Estonia and Lithuania (NOPHO), the UK (UKALL), the Netherlands (DCOG), Germany (COALL), Belgium (BSPHO), Ireland (PHOAI), Portugal (SHOP) and France (SFCE), EUDRACT number: 2018-001795-38. While the A2G protocol is detailed regarding the treatment of ALL and even offers guidance for the treatment of thrombosis, there are no recommendations on measurement of coagulation parameters, thromboprophylaxis or replacement of fibrinogen or antithrombin. We conducted a survey with the Nordic and Baltic centres participating in the A2G protocol to assess the current practices in the measurements of coagulation and thromboprophylaxis in children and young adults.

METHODS

An electronic survey was sent to all participating centres in the Nordic and Baltic countries (n = 34; NOPHO) in October 2021, with the possibility of replying up until January 2022. The survey included questions on the routine assessment of coagulation parameters, replacement of fibrinogen, thromboprophylaxis, and replacement of antithrombin as thromboprophylaxis or as treatment of thrombosis.

RESULTS

Of the 34 centres receiving the electronic survey, 29 (85%; 12 adult and 17 paediatric) completed the questionnaire, accounting for about 190 of the 230 patients (83%) with ALL expected to be included per year by the NOPHO group. For more detailed information on participating centres, see Table S1.

All but two centres (93%) measured coagulation parameters routinely at diagnosis, while only 59% (17/29) continued to assess coagulation parameters routinely (Table 1). The time points for routine follow-up assessment varied: in connection with asparaginase treatment (n = 1 and n = 6 for adult and paediatric centres, respectively), before lumbar puncture (LP) or other invasive procedures (n = 4; n = 2), 1–2 times weekly during induction (n = 1; n = 2, with adult centres continuing throughout the asparaginase treatment).

Fibrinogen replacement

Six of the seven adult and eight of the 10 paediatric centres with routine measurements of coagulation parameters after diagnosis replaced fibrinogen at low levels. In total, 17 of 29 (59%) centres replaced low fibrinogen: nine centres when measuring low fibrinogen levels (eight centres at routine measurements and one if occasionally measured), five before LP, in three centres only with bleeding. The cut-off for replacement was most often less than 1 g/l (n = 10) and was more often used in paediatric centres (n = 8) compared to adult centres (n = 2). Three centres replaced at less than 1–1.5 g/l and another two at less than 1.5 g/l (missing data n = 1). In two centres the decision was made individually. When comparing the countries, measuring and replacing fibrinogen was frequent in Finland where all centres measured and only one of the eight Finnish centres did not substitute fibrinogen prophylactically in any patient.

TABLE 1 Survey of routine laboratory assessment in 29 Nordic and Baltic Centres during treatment according to the ALLTogether (A2G) protocol in patients with ALL

	Paediatric centres (n = 17)	Adult centres (n = 12)
Routine laboratory assessment of haemostasis at diagnosis	15	12
aPTT	15	12
INR	14	12
Fibrinogen	8	11
Antithrombin	5	5
Protein C	2	1
Protein S	2	1
D-dimer	2	5
Prothrombin time	1	1
Factor V Leiden and prothrombin gene mutation	2	0
Factor VIII	1	0
Thrombin time	1	1
FIDD	0	2
Routine laboratory assessment of haemostasis after diagnosis	10	7
aPTT	8	7
INR	7	7
Fibrinogen	8	5
Antithrombin	8	4
D-dimer	0	2
Prothrombin time	1	0
Factor VIII	1	0
Thrombin time	1	1
FIDD	0	1

Abbreviations: aPTT, activated partial thromboplastin time; FIDD, fibrin degradation products; INR, international normalised ratio.

TABLE 2 Clinical practice on assessment of coagulation, replacement of antithrombin and fibrinogen and thromboprophylaxis during A2G treatment in 29 Nordic and Baltic Centres

	Paediatric centres (n=17)	Adult centres (n=12)
Routine laboratory assessment of haemostasis		
At diagnosis	17	12
After diagnosis	10	7
Thromboprophylaxis		
Given to all patients at the centre	0	8
Given to high-thrombosis-risk patients	2[a]	3[b]
Not given	15	1
Follow-up of antithrombin measurement after diagnosis		
Done in all patients	7	3
Done in selected patients[a]	5	3
Not performed	5	6
Prophylactic antithrombin used to prevent DVT		
Given to all patients at the centre	2	1
Given to selected patients	4	1
Not given	10	10
Missing data	1	0
Antithrombin replacement used after DVT		
Given to all patients at the centre	4	3
Given to selected patients	5	2
Not given	8	7
Follow-up of fibrinogen after diagnosis		
All patients	7	5
Not performed	10	7
Prophylactic fibrinogen replacement to prevent bleeds		
Given to all patients at the centre	4	2
Given to selected patients	6	5
Not given	5	5
Missing data	2	0

Abbreviation: DVT, deep vein thrombosis.

[a]One centre in teenagers with mediastinal mass and one in case of mediastinal mass/previous thrombosis/intensive care/femoral central venous catheter.

[b]High-risk arm/previous thrombosis/based on coagulation parameters.

Thromboprophylaxis and antithrombin replacement

All but one adult centre (11/12; 92%) used thromboprophylaxis: eight of 12 adult centres (67%) used thromboprophylaxis for all patients during induction with three centres continuing until the last asparaginase treatment. Three centres (3/12; 25%) used thromboprophylaxis in selected patients (Table 2). All centres used LMWH in prophylactic dosing, and no DOACs were used. Two adult centres (2/12; 17%) with routine antithrombin measurements after diagnosis also replaced antithrombin with a cut-off of 50%.

In contrast, no paediatric centres used LMWH for thromboprophylaxis routinely in all patients, and only two centres (2/17; 12%) used prophylactic LMWH in selected patients (Table 2). No DOACs were used in children for thromboprophylaxis. Antithrombin replacement at low levels was used as the only thromboprophylaxis in six paediatric centres (6/17; 35%, missing data n = 1). Cut-offs for antithrombin replacement varied: less than 30% (n = 1), 40% (n = 3) and 55% (n = 1) for all children under asparaginase and less than 75% in children aged over 6 years old during induction (n = 1).

Like with fibrinogen, measuring and replacing antithrombin was mostly performed in Finland compared to other countries, all Finnish centres measured and only one of the eight centres did not substitute antithrombin prophylactically in any patients.

After a thrombotic event, 14 of 29 centres (5/12 adult, 9/17 paediatric) replaced low antithrombin levels (cut-offs <50% n = 4; <55% n = 1; <60% n = 2; <70% n = 2; <75% n = 2,

individual $n = 1$, missing data $n = 2$). Duration of antithrombin replacement after a thrombosis varied: first weeks, until last asparaginase, always if below 60%, until thrombosis treatment is terminated and with five centres answering, "not known".

The centres that followed coagulation parameters after diagnosis (17/29 centres) were more likely to use thromboprophylaxis (7/17; 41%) and replace fibrinogen (14/17; 82%) or antithrombin at low levels both as thromboprophylaxis (8/17; 47%) and after thrombosis (11/17; 65%).

DISCUSSION

This survey on coagulation among 29 Nordic and Baltic cancer centres using the same leukaemia treatment protocol for children and young adults revealed a high degree of variation in routine procedures regarding measurement of coagulation parameters, replacement of fibrinogen and antithrombin, and thromboprophylaxis. At diagnosis, both paediatric and adult centres measured coagulation parameters, but after diagnosis measurements, timing differed significantly. Centres that regularly measured antithrombin and fibrinogen levels after diagnosis were more likely to replace these at low levels, most likely due to a local hospital policy on measurement and replacement. A cut-off of 1.0 g/l was often used for fibrinogen replacement, as per international transfusion guidelines.

As expected, DOACs were not used in children for thromboprophylaxis. However, adult centres with often greater experience with DOACs in general did not use them as thromboprophylaxis either. The long practice of using LMWH in ALL patients and its short half-life allowing dose reduction with decreasing platelet count may explain the preference for LMWH. Furthermore, subcutaneous injections are generally more feasible in adults rather than children. However, since the incidence of thrombosis in teenagers and young adults with T-cell-ALL has been shown to be as high as 20%, thromboprophylaxis could be beneficial in these patients and prediction models have been published to identify children at the highest risk.[1,3]

A previous randomised study including 949 children with ALL, the Thrombotect study, assessed the effect of thromboprophylaxis in three arms: a standard arm in which patients received low-dose unfractionated heparin infusions while hospitalised, an experimental arm in which patients received LMWH in prophylactic dose, and a second experimental arm in which patients received antithrombin replacement at levels below normal.[9] Thromboembolism occurred in 8.0% in the standard arm compared to 3.5% in the LMWH arm ($p = 0.011$) and 1.9% in the antithrombin arm ($p < 0.001$). The authors concluded that prophylactic use of antithrombin or LMWH significantly reduced the risk of thromboembolism. In our survey the use of thromboprophylaxis varied between paediatric and adult centres with almost all adult and none of the paediatric centres using LMWH as thromboprophylaxis, while six paediatric centres relied on antithrombin replacement to prevent thrombosis.

Our findings are in line with a recently published survey of American paediatric oncologists on management practices of asparaginase-related coagulopathy in children.[10] Only 5% (n = 13/285) of the doctors routinely prescribed prophylactic anticoagulation during leukaemia induction treatment, while 51% measured baseline coagulation. A total of 46% of physicians replaced low fibrinogen most often at a cut-off of 1 g/l and 14% replaced low antithrombin with a median antithrombin cut-off activity level of 60%. This significant variation in practices of American paediatric oncologists for monitoring and management of asparaginase-associated haemostatic disorders resembles our findings. Evidence-based guidelines could help to standardise and evaluate clinical practices.

Several large leukaemia treatment consortiums have published results on the incidence, risk factors and outcome of thrombosis without regarding different practices on thromboprophylaxis. This survey can be seen as a first step to aid assessing the outcome in different centres within the A2G consortium but should be expanded to all centres participating in the A2G protocol. While there are no evidence-based guidelines for thromboprophylaxis, especially in children with ALL, expert opinions within consortiums could be utilised to standardise the practices between several treatment centres. Comparing the outcome between the consortiums with different practices could assist future common guidelines.

AUTHOR CONTRIBUTIONS

All authors participated in data collection. N.G. Andersson and S. Ranta are responsible for the concept and study design, analysis of the data and drafting of the manuscript. All authors took part in the interpretation of the data and critical revising of the manuscript. All authors reviewed the manuscript and gave it their final approval.

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CONFLICT OF INTEREST

All authors report no conflicts of interest for this study.

DATA AVAILABILITY STATEMENT

The survey was sent out by the Nordic Society of Paediatric Haematology and Oncology (NOPHO) thrombosis group and captured in a Redcap database. The data from that survey that support the findings of this study are available from the authors.

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REFERENCES

1. Tuckuviene R, Ranta S, Albertsen BK, Andersson NG, Bendtsen MD, Frisk T, et al. Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study. J Thromb Haemost. 2016;14:485–94.
2. Ranta S, Tuckuviene R, Makipernaa A, Albertsen BK, Frisk T, Tedgard U, et al. Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia - a multicentre study from the Nordic Society of Paediatric Haematology and Oncology. Br J Haematol. 2015;168:547–52.
3. Mitchell L, Lambers M, Flege S, Kenet G, Li-Thiao-Te V, Holzhauer S, et al. Validation of a predictive model for identifying an increased risk for thromboembolism in children with acute lymphoblastic leukemia: results of a multicenter cohort study. Blood. 2010;115:4999–5004.
4. Athale UH, Chan AK. Thromboembolic complications in pediatric hematologic malignancies. Semin Thromb Hemost. 2007;33:416–26.
5. Grace RF, Dahlberg SE, Neuberg D, Sallan SE, Connors JM, Neufeld EJ, et al. The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. Br J Haematol. 2011;152:452–9.
6. Alqasim AMZ, Al-Hadithi RH, Al-Khalidi AN. Coagulopathic side effect of L-asparaginase on fibrinogen level in childhood acute lymphoblastic leukemia during induction phase. Hematol Oncol Stem Cell Ther. 2019;12:67–9.
7. Hunault-Berger M, Chevallier P, Delain M, Bulabois CE, Bologna S, Bernard M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. Haematologica. 2008;93:1488–94.
8. Kwaan HC. Double hazard of thrombophilia and bleeding in leukemia. Hematology. 2007;2007:151–7.
9. Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, et al. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica. 2019;104:756–65.
10. Greenmyer JR, Wyatt KD, Rodriguez V, Ashrani AA, Warad D. Management practices for asparaginase-associated coagulopathy: a survey of pediatric oncologists. J Pediatr Hematol Oncol. 2022. https://doi.org/10.1097/MPH.0000000000002396

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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